Isoquinoline derivatives

The present invention relates to isoquinoline derivatives, isoquinoline derivatives as medicaments, isoquinoline derivatives as inhibitors of one or more kinases, the use of isoquinoline derivatives for the manufacture of a pharmaceutical, a method for producing a pharmaceutical composition containing said isoquinoline derivatives, the pharmaceutical composition obtainable by said method and a method of treatment, comprising administering said pharmaceutical composition.

Protein phosphorylation is a fundamental process for the regulation of cellular functions. The coordinated action of both protein kinases and phosphatases controls the levels of phosphorylation and, hence, the activity of specific target proteins. One of the predominant roles of protein phosphorylation is in signal transduction, where extracellular signals are amplified and propagated by a cascade of protein phosphorylation and dephosphorylation events, e.g. in the $p21^{ras}$/raf pathway.

The $p21^{ras}$ gene was discovered as an oncogene of the Harvey (rasH) and Kirsten (rasK) rat sarcoma viruses. In humans, characteristic mutations in the cellular ras gene (c-ras) have been associated with many different types of cancers. These mutant alleles, which render Ras constitutively active, have been shown to transform cells, such as the murine cell line NIH 3T3, in culture.

The $p21^{ras}$ oncogene is a major contributor to the development and progression of human solid cancers and is mutated in 30 % of all human cancers (Bolton et al. (1994) Ann. Rep. Med. Chem., 29, 165-74; Bos. (1989) Cancer Res., 49, 4682-9). Oncogenic Ras mutations have been identified for example in lung cancer, colorectal cancer, pancreas, thyroid cancer, melanoma, bladder tumours, liver tumour, kidney tumor, dermatological tumours and haematological tumors (Ddjei et al. (2001), J. Natl. Cancer Inst.

93(14), 1062-74; Midgley, R.S. and Kerr, D.J. (2002) Critical Rev. Onc/ hematol 44, 109-120; Downward, J. (2003), Nature reviews 3, 11-22). In its normal, unmutated form, the ras protein is a key element of the signal transduction cascade directed by growth factor receptors in almost all tissues (Avruch et al. (1994) Trends Biochem. Sci., 19, 279-83).

Biochemically, ras is a guanine nucleotide binding protein, and cycling between a GTP-bound activated and a GDP-bound resting form is strictly controlled by ras endogenous GTPase activity and other regulatory proteins. The ras gene product binds to guanine triphosphate (GTP) and guanine diphosphate (GDP) and hydrolyzes GTP to GDP. It is the GTP-bound state of Ras that is active. In the ras mutants in cancer cells, the endogenous GTPase activity is alleviated and, therefore, the protein delivers constitutive growth signals to downstream effectors such as the enzyme raf kinase. This leads to the cancerous growth of the cells which carry these mutants (Magnuson et al. (1994) Semin. Cancer Biol., 5, 247-53). The ras proto-oncogene requires a functionally intact c-raf1 proto-oncogene in order to transduce growth and differentiation signals initiated by receptor and non-receptor tyrosine kinases in higher eukaryotes.

Activated Ras is necessary for the activation of the c-raf-1 proto-oncogene, but the biochemical steps through which Ras activates the Raf-1 protein (Ser/Thr) kinase are now well characterized . It has been shown that inhibiting the effect of active ras by inhibiting the raf kinase signaling pathway by administration of deactivating antibodies to raf kinase or by co-expression of dominant negative raf kinase or dominant negative MEK, the substrate of raf kinase, leads to the reversion of transformed cells to the normal growth phenotype see: Daum et al. (1994) Trends Biochem. Sci., 19, 474-80; Fridman et al. (1994) J Biol. Chem., 269, 30105-8. Kolch et al. (1991) Nature, 349, 426-28) and for review Weinstein-Oppenheimer et al. Pharm. & Therap. (2000), 88, 229-279.

Similarly, inhibition of raf kinase (by antisense oligodeoxynucleotides) has been correlated in vitro and in vivo with inhibition of the growth of a variety of human tumor types (Monia et al., Nat. Med. 1996, 2, 668-75; Geiger et al. (1997), Clin. Cancer Res. 3(7): 1179-85; Lau et al. (2002), Antisense Nucl. Acid. Drug Dev. 12(1): 11-20 ; McPhillips et al. (2001), Br. J. Cancer 85(11): 1753-8).

Raf serine- and threonine-specific protein kinases are cytosolic enzymes that stimulate cell growth in a variety of cell systems (Rapp, U.R., et al. (1988) in The oncogene handbook; T. Curran, E.P. Reddy, and A. Skalka (ed.) Elsevier Science Publishers; The Netherlands, pp. 213-253; Rapp, U.R., et al. (1988) Cold Spring Harbor Sym. Quant. Biol. 53:173-184; Rapp, U.R., et al. (1990) Inv Curr. Top. Microbiol. Amunol. Potter and Melchers (eds), Berlin, Springer-Verlag 166:129-139).

Three isozymes have been characterized:

c-Raf (also named Raf-1, c-raf-1 or c-raf1) (Bonner, T.I., et al. (1986) Nucleic Acids Res. 14:1009-1015). A-Raf (Beck, T.W., et al. (1987) Nucleic Acids Res. 15:595-609), and B-Raf (Qkawa, S., et al. (1998) Mol. Cell. Biol. 8:2651-2654; Sithanandam, G. et a. (1990) Oncogene:1775). These enzymes differ in their expression in various tissues. Raf-1 is expressed in all organs and in all cell lines that have been examined, and A- and B-Raf are expressed in urogenital and brain tissues, respectively (Storm, S.M. (1990) Oncogene 5:345-351).

Raf genes are proto-oncogenes: they can initiate malignant transformation of cells when expressed in specifically altered forms. Genetic changes that lead to oncogenic activation generate a constitutively active protein kinase by removal or interference with an N-terminal negative regulatory domain of the protein (Heidecker, G., et al. (1990) Mol. Cell. Biol. 10:2503-2512; Rapp, U.R., et al. (1987) in Oncogenes and cancer S. A. Aaronson, J. Bishop, T. Sugimura, M. Terada, K. Toyoshima, and P. K. Vogt (ed). Japan Scientific

Press, Tokyo). Microinjection into NIH 3T3 cells of oncogenically activated but not wild-type versions of the Raf-protein prepared with Escherichia coli expression vectors results in morphological transformation and stimulates DNA synthesis (Rapp, U.R., et al. (1987) in Oncogenes and cancer; S. A. Aaronson, J. Bishop, T. Sugimura, M. Terada, K. Toyoshima, and P. K. Vogt (ed.) Japan Scientific Press, Tokyo; Smith, M. R., et al (1990) Mol. Cell. Biol. 10:3828-3833). Activating mutants of B-Raf have been identified in a wide range of human cancers e.g. colon, ovarien, melanomas and sarcomas (Davies, H., et al. (2002), Nature 417 949-945. Published online June 9, 2002, 10.1038/nature00766). The preponderant mutation is a single phosphomimetic substitution in the kinase activation domain (V599E), leading to constitutive kinase activity and transformation of NIH3T3 cells.

Thus, activated Raf-1 is an intracellular activator of cell growth. Raf-1 protein serine kinase in a candidate downstream effector of mitogen signal transduction, since Raf oncogenes overcome growth arrest resulting from a block of cellular ras activity due either to a cellular mutation (ras revertant cells) or microinjection of anti-ras antibodies (Rapp, U.R., et al. (1988) in The Oncogene Handbook, T. Curran, E.P. Reddy, and A. Skalka (ed.), Elsevier Science Publishers; The Netherlands, pp. 213-253; Smith, M.R., et al. (1986) Nature (London) 320:540-543).

c-Raf function is required for transformation by a variety of membrane-bound oncogenes and for growth stimulation by mitogens contained in serums (Smith, M.R., et al. (1986) Nature (London) 320:540-543). Raf-1 protein serine kinase activity is regulated by mitogens via phosphorylation (Morrison, D.K., et al. (1989) Cell 58:648-657), which also effects sub cellular distribution (Olah, Z., et al. (1991) Exp. Brain Res. 84:403; Rapp, U.R., et al. (1988) Cold Spring Harbor Sym. Quant. Biol. 53:173-184. Raf-1 activating growth factors include platelet-derived growth factor (PDGF) (Morrison, D.K., et al. (1988) Proc. Natl. Acad. Sci. USA 85:8855-8859), colony-stimulating factor (Baccarini, M., et al. (1990) EMBO J. 9:3649-3657), insulin

(Blackshear, P.J., et al. (1990) J. Biol. Chem. 265:12115-12118), epidermal growth factor (EGF) (Morrison, R.K., et al. (1988) Proc. Natl. Acad. Sci. USA 85:8855-8859), interleukin 2 (Turner, B.C., et al (1991) Proc. Natl. Acad. Sci. USA 88:1227), and interleukin 3 and granulocytemacrophage colony-stimulating factor (Carroll, M.P., et al (1990) J. Biol. Chem. 265:19812-19817).

Upon mitogen treatment of cells, the transiently activated Raf-1 protein serine kinase translocates to the perinuclear area and the nucleus (Olah, Z., et al. (1991) Exp. Brain Res. 84:403; Rapp, U.R., et al. (1988) Cold Spring Habor Sym. Quant. Biol. 53:173-184). Cells containing activated Raf are altered in their pattern of gene expression (Heidecker, G., et al. (1989) in Genes and signal transduction in multistage carcinogenesis, N. Colburn (ed.), Marcel Dekker, Inc., New York, pp. 339-374), and Raf oncogenes activate transcription from Ap-I/PEA3-dependent promoters in transient transfection assays (Jamal, S., et al (1990) Science 344:463-466; Kaibuchi, K., et al (1989) J. Biol. Chem. 264:20855-20858; Wasylyk, C., et al. (1989) Mol. Cell. Biol. 9:2247-2250).

There are at least two independent pathways for Raf-1 activation by extracellular mitogens: one involving protein kinase C (KC) and a second initiated by protein tyrosine kinases (Blackshear, P.J., et al. (1990) J. Biol. Chem. 265:12131-12134; Kovacina, K.S., et al (1990) J. Biol. Chem. 265:12115-12118; Morrison, D.K., et al. (1988) Proc. Natl. Acad. Sci. USA 85:8855-8859; Siegel, J.N., et al (1990) J. Biol. Chem. 265:18472-18480; Turner, B.C., et al (1991) Proc. Natl. Acad. Sci. USA 88:1227). In either case, activation involves Raf-1 protein phosphorylation. Raf-1 phosphorylation may be a consequence of a kinase cascade amplified by autophosphorylation or may be caused entirely by autophosphorylation initiated by binding of a putative activating ligand to the Raf-1 regulatory domain, analogous to PKC activation by diacylglycerol (Nishizuka, Y. (1986) Science 233:305-312).

The process of angiogenesis is the development of new blood vessels, generally capillaries, from pre-existing vasculature. Angiogenesis is defined as involving (i) activation of endothelial cells; (ii) increased vascular permeability; (iii) subsequent dissolution of the basement membrane and extravisation of plasma components leading to formation of a provisional fibrin gel extracellular matrix; (iv) proliferation and mobilization of endothelial cells; (v) reorganization of mobilized endothelial cells to form functional capillaries; (vi) capillary loop formation; and (vii) deposition of basement membrane and recruitment of perivascular cells to newly formed vessels.

Normal angiogenesis is activated during tissue growth, from embryonic development through maturity, and then enters a period of relative quiescence during adulthood.

Normal angiogensesis is also activated during wound healing, and at certain stages of the female reproductive cycle. Inappropriate or pathological angiogenesis has been associated with several disease states including various retinopathies; ischemic disease; atherosclerosis; chronic inflammatory disorders; rheumatoid arthritis, and cancer. The role of angiogenesis in disease states is discussed, for instance, in Fan et al, Trends in Pharmacol Sci. 16:54 66; Shawver et al, DOT Vol. 2, No. 2 February 1997; Folkmann, 1995, Nature Medicine 1:27-31.

In cancer the growth of solid tumors has been shown to be angiogenesis dependent. (See Folkmann, J., J. Nat'l. Cancer Inst., 1990, 82, 4-6.) Consequently, the targeting of pro-angiogenic pathways is a strategy being widely pursued in order to provide new therapeutics in these areas of great, unmet medical need.

Raf is involved in angiogenic processes. Endothelial growth factors (e.g. vascular endothelial growth factor VEGF or basic fibroblast growth factor bFGF) activates receptor tyrosine kinases (e.g. VEGFR-2) and signal through

the Ras/Raf/Mek/Erk kinase cascade and protects endothelial cells from apoptosis (Alavi et al. (2003), Science 301, 94-96; Hood, J.D. et al. (2002), Science 296, 2404; Mikula, M. et al. (2001), EMBO J. 20, 1952; Hauser, M. et al. (2001), EMBO J. 20, 1940; Wojnowski et al. (1997), Nature Genet. 16, 293). Activation of VEGFR-2 by VEGF is a critical step in the signal transduction pathway that initiates tumor angiogenesis. VEGF expression may be constitutive to tumor cells and can also be upregulated in response to certain stimuli. One such stimuli is hypoxia, where VEGF expression is upregulated in both tumor and associated host tissues. The VEGF ligand activates VEGFR-2 by binding with its extracellular VEGF binding site. This leads to receptor dimerization of VEGFRs and autophosphorylation of tyrosine residues at the intracellular kinase domain of VEGFR- 2. The kinase domain operates to transfer a phosphate from ATP to the tyrosine residues, thus providing binding sites for signaling proteins downstream of VEGFR-2 leading ultimately to initiation of angiogenesis (McMahon, G., The Oncologist, Vol. 5, No. 90001, 3-10, April 2000).

Mice with a targeted disruption in the Braf gene die of vascular defects during development (Wojnowski, L. et al. 1997, Nature genetics 16, page 293- 296). These mice show defects in the formation of the vascular system and in angiogenesis e.g. enlarged blood vessels and increased apoptotic death of differentiated endothelial cells.

For the identification of a signal transduction pathway and the detection of cross talks with other signaling pathways suitable models or model systems have been generated by various scientists, for example cell culture models (e.g. Khwaja et al., EMBO, 1997, 16, 2783-93) and transgenic animal models (e.g. White et al., Oncogene, 2001, 20, 7064-7072). For the examintion of particular steps in the signal transduction cascade, interfering compounds can be used for signal modulation (e.g. Stephens et al., Biochemical J., 2000, 351, 95-105). The compounds according to the invention may also be useful as reagents for the examination of kinase dependent signal transduction

pathways in animal and/or cell culture models or any of the clinical disorders listed throughout this application.

The measurement of kinase activity is a well known technique feasible for each person skilled in the art. Generic test systems for kinase activity detection with substrates, for example histone (e.g. Alessi et al., FEBS Lett. 1996, 399, 3, page 333-8) or myelin basic protein are well described in the literature (e.g. Campos-González, R. and Glenney, Jr., J.R. 1992 J. Biol. Chem. 267, Page 14535).

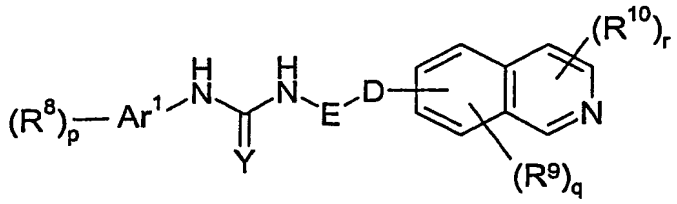
For the identification of kinase inhibitors various assay systems are available (see for example Walters et al., Nature Drug Discovery 2003, 2; page 259-266). For example, in scintillation proximity assays (e.g. Sorg et al., J. of. Biomolecular Screening, 2002, 7, 11-19) or flashplate assays the radioactive phosphorylation of a protein or peptide as substrate with γATP can be measured. In the presence of an inhibitory compound no signal or a decreased radioactive signal is detectable. Furthermore homogeneous time-resolved fluorescence resonance energy transfer (HTR-FRET), and fluorescence polarization (FP) technologies are useful for assay methods (for example Sills et al., J. of Biomolecular Screening, 2002, 191-214).

Other non-radioactive ELISA based assay methods use specific phospho-antibodies (AB). The phospho-AB binds only the phosphorylated substrate. This binding is detectable with a secondary peroxidase conjugated antibody, measured for example by chemiluminescence (for exaple Ross et al., Biochem. J., 2002, 366, 977-981).

The present invention provides compounds generally described as isoquinoline derivatives, including both aryl and/or heteroaryl derivatives which are preferably kinase inhibitors and more preferably inhibitors of the enzyme raf kinase. Since the enzyme is a downstream effector of $p21^{ras}$, the inhibitors preferably are useful in pharmaceutical compositions for human or

veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of tumors and/or cancerous cell growth mediated by raf kinase. In particular, the compounds preferably are useful in the treatment of human or animal solid cancers, e.g. murine cancer, since the progression of these cancers is dependent upon the ras protein signal transduction cascade and therefore susceptible to treatment by interruption of the cascade, i.e., by inhibiting raf kinase. Accordingly, the compound of Formula I or a pharmaceutically acceptable salt thereof can be administered for the treatment of diseases mediated by the raf kinase pathway especially cancers, preferably solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma), pathological angiogenesis and metastatic cell migration. Furthermore the compounds preferably are useful in the treatment of complement activation dependent chronic inflammation (Niculescu et al. (2002) Immunol. Res., 24:191-199) and HIV-1 (human immunodeficiency virus type1) induced immunodeficiency (Popik et al. (1998)J Virol, 72: 6406-6413) and infection disease, Influenza A virus (Pleschka, S. et al. (2001), Nat. Cell. Biol, 3(3):301-5) and Helicobacter pylori infection (Wessler, S. et al. (2002), FASEB J., 16(3): 417-9).

Therefore, subject of the present invention are isoquinoline derivatives of formula I



I

wherein

Ar^1 is selected from aromatic hydrocarbons containing 6 to 14 carbon atoms and ethylenical unsaturated or aromatic

heterocyclic residues containing 3 to 10 carbon atoms and one or two heteroatoms, independently selected from N, O and S,

E is $(CR^5R^6)_n$, wherein n is 1 or 2,

D is $(CR^5R^6)_k$, wherein k is 0 or 1,

R^5, R^6 are in each case independently from one another selected from H and A;

R^8, R^9 and R^{10} are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, $C(Hal)_3$, NO_2, $(CH_2)_nCN$, OHet, $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$, $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nOC(O)R^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$, CH=N-OA, CH_2CH=N-OA, $(CH_2)_nNHOA$, $(CH_2)_nCH$=N-R^{11}, $(CH_2)_nOC(O)NR^{11}R^{12}$, $(CH_2)_nNR^{11}COOR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$, $(CH_2)_nN(R^{11})C(R^{13})HCOOR^{12}$, $(CH_2)_nN(R^{11})C(R^{13})HCOR^{11}$, $(CH_2)_nN(R^{11})CH_2CH_2N(R^{12})CH_2COOR^{11}$, $(CH_2)_nN(R^{11})CH_2CH_2NR^{11}R^{12}$, $CH=CHCOOR^{13}$, $CH=CHCH_2NR^{11}R^{12}$, $CH=CHCH_2NR^{11}R^{12}$,

$CH=CHCH_2OR^{13}$, $(CH_2)_nN(COOR^{13})COOR^{14}$, $(CH_2)_nN(CONH_2)COOR^{13}$, $(CH_2)_nN(CONH_2)CONH_2$, $(CH_2)_nN(CH_2COOR^{13})COOR^{14}$, $(CH_2)_nN(CH_2CONH_2)COOR^{13}$, $(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^{13}COR^{14}$, $(CH_2)_nCHR^{13}COOR^{14}$, $(CH_2)_nCHR^{13}CH_2OR^{14}$, $(CH_2)_nOCN$ and $(CH_2)_nNCO$, wherein

R^{11}, R^{12} are independently selected from a group consisting of H, A, $(CH_2)_mAr^3$ and $(CH_2)_mHet$, or in $NR^{11}R^{12}$,

R^{11} and R^{12} form, together with the N-atom they are bound to, a 5-, 6- or 7- membered heterocyclus which optionally contains 1 or 2 additional hetero atoms, selected from N, O and S,

R^{13}, R^{14} are independently selected from a group consisting of H, Hal, A, $(CH_2)_mAr^4$ and $(CH_2)_mHet$,

A is selected from the group consisting of alkyl, alkenyl, cycloalkyl, alkylenecycloalkyl, alkoxy, alkoxyalkyl and saturated heterocyclyl, preferably from the group consisting of alkyl, alkenyl, cycloalkyl, alkylenecycloalkyl, alkoxy and alkoxyalkyl,

Ar^3, Ar^4 are independently from one another aromatic hydrocarbon residues comprising 5 to 12 and preferably 5 to 10 carbon atoms which are optionally substituted by one or more substituents, selected from a group consisting of A, Hal, NO_2, CN, OR^{15}, $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15}, $SO_2NR^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$,

Het	is a saturated, unsaturated or aromatic heterocyclic residue which is optionally substituted by one ore more substituents, selected from a group consisting of A, Hal, NO_2, CN, OR^{15}, $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15}, $SO_2NR^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$,
R^{15}, R^{16}	are independently selected from a group consisting of H, A, and $(CH_2)_mAr^6$, wherein
Ar^6	is a 5- or 6-membered aromatic hydrocarbon which is optionally substituted by one or more substituents selected from a group consisting of methyl, ethyl, propyl, 2-propyl, tert.-butyl, Hal, CN, OH, NH_2 and CF_3,
k, n and m	are independently of one another 0, 1, 2, 3, 4, or 5,
Y	is selected from O, S, NR^{21}, $C(R^{22})$-NO_2, $C(R^{22})$-CN and $C(CN)_2$, wherein
R^{21}	is independently selected from the meanings given for R^{13}, R^{14} and
R^{22}	is independently selected from the meanings given for R^{11}, R^{12},
p, r	are independently from one another 0, 1, 2, 3, 4 or 5,
q	is 0, 1, 2, 3 or 4, preferably 0, 1 or 2,
u	is 0, 1, 2 or 3, preferably 0, 1 or 2,

and

Hal is independently selected from a group consisting of F, Cl, Br and I;

and the pharmaceutically acceptable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios, and more preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

As used herein, the term "alkyl" preferably refers to a straight or branched chain hydrocarbon having from one to twelve carbon atoms, optionally substituted with substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or C_1-C_6 perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, and the like.

As used herein, the term "C_1-C_6 alkyl" preferably refers to an alkyl group as defined abovecontaining at least 1, and at most 6, carbon atoms. Examples of branched or straight chained "C_1-C_6 alkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, isobutyl, n-butyl, t-butyl, n-pentyl and isopentyl.

As used herein, the term "alkylene" preferably refers to a straight or branched chain divalent hydrocarbon radical having from one to ten carbon atoms, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl, optionally substituted by alkyl, nitro, cyano, halogen and lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, n-propylene, n-butylene and the like.

As used herein, the term "C_1-C_6 alkylene" preferably refers to an alkylene group, as defined above, which contains at least 1, and at most 6, carbon atoms respectively. Examples of "C_1-C_6 alkylene" groups useful in the present invention include, but are not limited to, methylene, ethylene and n-Propylene.

As used herein, the term "halogen" or "hal" preferably refers to fluorine (F), chlorine (Cl), bromine (Br) or iodine (I).

As used herein, the term "C_1-C_6 haloalkyl" preferably refers to an alkyl group as defined above containing at least 1, and at most 6, carbon atoms substituted with at least one halogen, halogen being as defined herein. Examples of branched or straight chained "C_1-C_6 haloalkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl and n-butyl substituted independently with one or more halogens, e.g., fluoro, chloro, bromo and iodo.

As used herein, the term "cycloalkyl" or "C_3-C_7 cycloalkyl" preferably refers to a non-aromatic cyclic hydrocarbon ring having from three to seven carbon atoms and which optionally includes a C_1-C_6 alkyl linker through which it may be attached. The C_1-C_6 alkyl group is as defined above. Exemplary "C_3-C_7 cycloalkyl" groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The term "cycloalkyl", as used herein preferably also includes saturated heterocyclic groups, which are preferably selected from the cycloalkyl-groups as defined above, wherein one or two carbon atoms are replaced by hetero atoms, selected from the group consisting of O, N and S, which optionally is substituted by one or more substituents, preferably selected from alkyl, =O, =S and substituted or unsubstituted imino groups.

As used herein, the term "C_3-C_7 cycloalkylene" preferably refers to a non-aromatic alicyclic divalent hydrocarbon radical having from three to seven carbon atoms, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "cycloalkylene" as used herein include, but are not limited to, cyclopropyl-1,1-diyl, cyclopropyl-1,2-diyl, cyclobutyl-1,2-diyl, cyclopentyl-1,3-diyl, cyclohexyl-1,4-diyl, cycloheptyl-1,4-diyl, or cyclooctyl-1,5-diyl, and the like.

As used herein, the term "heterocyclic" or the term "heterocyclyl" preferably refers to a three to twelve-membered heterocyclic ring having one or more degrees of unsaturation containing one or more heteroatomic substitutions selected from S, SO, SO_2, O or N, optionally substituted with substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 haloalkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6

alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or C_1-C_6 perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more other "heterocyclic" ring(s) or cycloalkyl ring(s). Examples of "heterocyclic" moieties include, but are not limited to, tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane, pyrrolidine, piperidine, morpholine, tetrahydrothiopyran, tetrahydrothiophene, and the like.

As used herein, the term "heterocyclylene" preferably refers to a three to twelve-membered heterocyclic ring diradical having one or more degrees of unsaturation containing one or more heteroatoms selected from S, SO, SO_2, O or N, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, lower perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more benzene rings or to one or more of another "heterocyclic" rings or cycloalkyl rings. Examples of "heterocyclylene" include, but are not limited to, tetrahydrofuran-2,5-diyl, morpholine-2,3-diyl, pyran-2,4-diyl, 1,4-dioxane-2,3-diyl, 1,3-dioxane-2,4-diyl, piperidine-2,4-diyl, piperidine-1,4-diyl, pyrrolidine-1,3-diyl, morpholine-2,4-diyl, and the like.

As used herein, the term "aryl" preferably refers to an optionally substituted benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene rings to form, for example, anthracene, phenanthrene, or napthalene ring systems. Exemplary optional substituents include C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl,

acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, C_1-C_6 perfluoroalkyl, heteroaryl, or aryl, multiple degrees of substitution being allowed. Examples of "aryl" groups include, but are not limited to Phenyl, 2-naphthyl, 1-naphthyl, biphenyl, as well as substituted derivatives thereof.

As used herein, the term "arylene" preferably refers to a benzene ring diradical or to a benzene ring system diradical fused to one or more optionally substituted benzene rings, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl and aryl, multiple degrees of substitution being allowed. Examples of "arylene" include, but are not limited to benzene-1,4-diyl, naphthalene-1,8-diyl, anthracene-1,4-diyl, and the like.

As used herein, the term "aralkyl" preferably refers to an aryl or heteroaryl group, as defined herein, attached through a C_1-C_6 alkyl linker, wherein C_1-C_6 alkyl is as defined herein. Examples of "aralkyl" include, but are not limited to, benzyl, phenylpropyl, 2-pyridylmethyl, 3-isoxazolylmethyl, 5-methyl-3-isoxazolylmethyl and 2-imidazolylethyl.

As used herein, the term "heteroaryl" preferably refers to a monocyclic five to seven-membered aromatic ring, or to a fused bicyclic aromatic ring system comprising two of such monocyclic five to seven-membered aromatic rings. These hetroaryl rings contain one or more nitrogen, sulfur and/or oxygen heteroatoms, where N-Oxides and sulfur Oxides and dioxides are permissible heteroatom substitutions and may be optionally substituted with up to three members selected from a group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 haloalkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by

alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, C_1-C_6 perfluoroalkyl, heteroaryl or aryl, multiple degrees of substitution being allowed. Examples of "heteroaryl" groups used herein include furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, oxo-pyridyl, thiadiazolyl, isothiazolyl, pyridyl, pyridazyl, pyrazinyl, pyrimidyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, indolyl, indazolyl, and substituted versions thereof.

As used herein, the term "heteroarylene" preferably refers to a five - to seven -membered aromatic ring diradical, or to a polycyclic heterocyclic aromatic ring diradical, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-Oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl, or aryl, multiple degrees of substitution being allowed. For polycyclic aromatic ring system diradicals, one or more of the rings may contain one or more heteroatoms. Examples of "heteroarylene" used herein are furan-2,5-diyl, thiophene-2,4-diyl, 1,3,4-oxadiazole-2,5-diyl, 1,3,4-thiadiazole-2,5-diyl, 1,3-thiazole-2,5-diyl, pyridine-2,4-diyl, pyridine-2,3-diyl, pyridine-2,5-diyl, pyrimidine-2,4-diyl, quinoline-2,3-diyl, and the like.

As used herein, the term "alkoxy" preferably refers to the group R_aO-, where R_a is alkyl as defined above and the term "C_1-C_6 alkoxy" preferably refers to an alkoxy group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms. Exemplary C_1-C_6 alkoxy groups useful in the

present invention include, but are not limited to methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and t-butoxy.

As used herein, the term "haloalkoxy" preferably refers to the group R_aO-, where R_a is haloalkyl as defined above and the term "C_1-C_6 haloalkoxy" preferably refers to an haloalkoxy group as defined herein wherein the haloalkyl moiety contains at least 1 and at most 6 carbon atoms. Exemplary C_1-C_6 haloalkoxy groups useful in the present invention include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and t-butoxy substituted with one or more halo groups, for instance trifluoromethoxy.

As used herein the term "aralkoxy" preferably refers to the group R_CR_BO-, where R_B is alkyl and R_C is aryl as defined above.

As used herein the term "aryloxy" preferably refers to the group R_CO-, where R_C is aryl as defined above.

As used herein, the term "alkylsulfanyl" preferably refers to the group R_AS-, where R_A is alkyl as defined above and the term "C_1-C_6 alkylsulfanyl" preferably refers to an alkylsulfanyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

As used herein, the term "haloalkylsulfanyl" preferably refers to the group R_DS-, where R_D is haloalkyl as defined above and the term "C_1-C_6 haloalkylsulfanyl" preferably refers to a haloalkylsulfanyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

As used herein, the term "alkylsulfenyl" preferably refers to the group $R_AS(O)$-, where R_A is alkyl as defined above and the term "C_1-C_6 alkylsulfenyl" preferably refers to an alkylsulfenyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

As used herein, the term "alkylsulfonyl" preferably refers to the group R_ASO_2-, where R_A is alkyl as defined above and the term "C_1-C_6 alkylsulfonyl" preferably refers to an alkylsulfonyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

As used herein, the term "oxo" preferably refers to the group =O.

As used herein, the term "mercapto" preferably refers to the group –SH.

As used herein, the term "carboxy" preferably refers to the group –COOH.

As used herein, the term "cyano" preferably refers to the group –CN.

As used herein, the term "cyanoalkyl" preferably refers to the group $-R_BCN$, wherein R_B is alkylen as defined above. Exemplary "cyanoalkyl" groups useful in the present invention include, but are not limited to, cyanomethyl, cyanoethyl and cyanoisopropyl.

As used herein, the term "aminosulfonyl" preferably refers to the group –SO_2NH_2.

As used herein, the term "carbamoyl" preferably refers to the group –$C(O)NH_2$.

As used herein, the term "sulfanyl" shall refer to the group –S-.

As used herein, the term "sulfenyl" shall refer to the group –S(O)-.

As used herein, the term "sulfonyl" shall refer to the group –$S(O)_2$- or -SO_2-.

As used herein, the term "acyl" preferably refers to the group $R_FC(O)$-, where R_F is alkyl, cycloalkyl or heterocyclyl as defined herein.

As used herein, the term "aroyl" preferably refers to the group $R_CC(O)$-, where R_C is aryl as defined herein.

As used herein, the term "heteroaroyl" preferably refers to the group $R_EC(O)$-, where R_E is heteroaryl as defined herein.

As used herein, the term "alkoxycarbonyl" preferably refers to the group $R_AOC(O)$-, where R_A is alkyl as defined herein.

As used herein, the term "acyloxy" preferably refers to the group $R_FC(O)O$-, where R_F is alkyl, cycloalkyl, or heterocyclyl as defined herein.

As used herein, the term "aroyloxy" preferably refers to the group $R_CC(O)O$-, where R_C is aryl as defined herein.

As used herein, the term "heteroaroyloxy" preferably refers to the group $R_EC(O)O$-, where R_E is heteroaryl as defined herein.

As used herein, the term "carbonyl" or "carbonyl moiety" preferably refers to the group C=O.

As used herein, the term "thiocarbonyl" or "thiocarbonyl moiety" preferably refers to the group C=S.

As used herein, the term "amino", "amino group" or "imino moiety" preferably refers to the group $NR_GR_{G'}$, wherein R_G and $R_{G'}$, are preferably selected, independently from one another, from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkenyl, cycloalkyl, alkylenecycloalkyl, cyanoalkyl, aryl, aralkyl, heteroaryl, acyl and aroyl. If both R_G and $R_{G'}$ are hydrogen,

$NR_GR_{G'}$ is also referred to as "unsubstituted amino moiety" or "unsubstituted amino group". If R_G and/or $R_{G'}$ are other than hydrogen, $NR_GR_{G'}$ is also referred to as "substituted amino moiety" or "substituted amino group".

As used herein, the term "imino" or "imino moiety" preferably refers to the group $C=NR_G$, wherein R_G is preferably selected from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkenyl, cycloalkyl, alkylenecycloalkyl, cyanoalkyl, aryl, aralkyl, heteroaryl, acyl and aroyl. If R_G is hydrogen, $C=NR_G$ is also referred to as "unsubstituted imino moiety". If R_G is a residue other than hydrogen, $C=NR_G$ is also referred to as "substituted imino moiety".

As used herein, the term "ethene-1,1-diyl moiety" preferably refers to the group $C=CR_KR_L$, wherein R_K and R_L are preferably selected, independently from one another, from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkenyl, cycloalkyl, nitro, alkylenecycloalkyl, cyanoalkyl, aryl, aralkyl, heteroaryl, acyl and aroyl. If both hydrogen R_K and R_L are hydrogen, $C=CR_KR_L$ is also referred to as "unsubstituted ethene-1,1-diyl moiety". If one of R_K and R_L or both are a residue other than hydrogen, $C=CR_KR_L$ is also referred to as "substituted ethene-1,1-diyl moiety".

As used herein, the terms "group", "residue" and "radical" or "groups", "residues" and "radicals" are usually used as synonyms, respectively, as it is common practice in the art.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s), which occur, and events that do not occur.

As used herein, the term "physiologically functional derivative" preferably refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example, an ester or an amide, which upon administration to a mammal is capable of providing (directly or indirectly) a

compound of the present invention or an active metabolite thereof. Such derivatives are clear to those skilled in the art, without undue experimentation, and with reference to the teaching of Burger's Medicinal Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent that it teaches physiologically functional derivatives.

As used herein, the term "solvate" preferably refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula I or a salt or physiologically functional derivative thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. Most preferably the solvent used is water.

As used herein, the term "substituted" preferably refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

Certain of the compounds described herein may contain one or more chiral atoms, or may otherwise be capable of existing as two or more stereoisomers, which are usually enantiomers and/or diastereomers. Accordingly, the compounds of this invention include mixtures of stereoisomers, especially mixtures of enantiomers, as well as purified stereoisomers, especially purified enantiomers, or stereoisomerically enriched mixtures, especially enantiomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by formulae I above as well as any wholly or partially equilibrated mixtures thereof. The present invention also covers the individual isomers of the compounds represented by the formulas above as

mixtures with isomers thereof in which one or more chiral Centers are inverted. Also, it is understood that all tautomers and mixtures of tautomers of the compounds of formulae I are included within the scope of the compounds of formulae I and preferably the formulae and subformulae corresponding thereto.

Racemates obtained can be resolved into the isomers mechanically or chemically by methods known per se. Diastereomers are preferably formed from the racemic mixture by reaction with an optically active resolving agent. Examples of suitable resolving agents are optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids, such as β-camphorsulfonic acid. Also advantageous is enantiomer resolution with the aid of a column filled with an optically active resolving agent (for example dinitrobenzoylphenylglycine); an example of a suitable eluent is a hexane/isopropanol/
acetonitrile mixture.

The diastereomer resolution can also be carried out by standard purification processes, such as, for example, chromatography or fractional crystallization.

It is of course also possible to obtain optically active compounds of the formula I by the methods described above by using starting materials which are already optically active.

Unless indicated otherwise, it is to be understood that reference to compounds of formula I preferably includes the reference to the compounds of formula I' and I''. Unless indicated otherwise, it is to be understood that reference to the compounds of formula I, I' and I'' preferably includes the reference to the sub formulae corresponding thereto, for example the sub formulae I.1 to I.16 and preferably formulae Ia to Ir. It is also understood that the following embodiments, including uses and compositions, although

recited with respect to formula I are preferably also applicable to formulae I', I'' and sub formulae I.1 to I.16 and preferably formulae Ia to Ir.

Even more preferred are compounds of formula I

wherein

Ar^1 is selected from aromatic hydrocarbons containing 6 to 10 and especially 6 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 8 and especially 4 to 6 carbon atoms and one or two heteroatoms, independently selected from N, O and S and especially selected from N and O,

R^8, R^9 and R^{10} are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, $C(Hal)_3$, NO_2, $(CH_2)_nCN$, OHet, $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$, $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, and/or are independently selected from a group consisting of $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nOC(O)R^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$, $(CH_2)_nNHOA$, $(CH_2)_nNR^{11}COOR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$, $(CH_2)_nN(R^{11})C(R^{13})HCOOR^{12}$, $(CH_2)_nN(R^{11})C(R^{13})HCOR^{11}$, $(CH_2)_nN(COOR^{13})COOR^{14}$,

$(CH_2)_nN(CONH_2)COOR^{13}$, $(CH_2)_nN(CONH_2)CONH_2$, $(CH_2)_nN(CH_2COOR^{13})COOR^{14}$, $(CH_2)_nN(CH_2CONH_2)COOR^{13}$, $(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^{13}COR^{14}$, $(CH_2)_nCHR^{13}COOR^{14}$ and $(CH_2)_nCHR^{13}CH_2OR^{14}$,

p is 1, 2, 3 or 4, preferably 1, 2 or 3, and

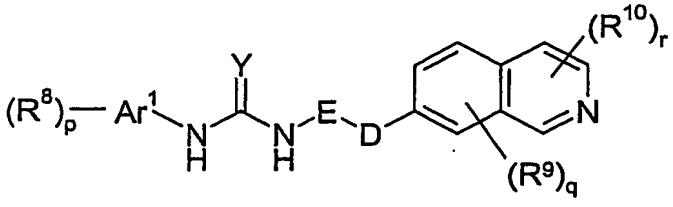
r is 0, 1, 2, or 3, preferably 0, 1 or 2;

and the pharmaceutically acceptable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios, and more preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

Subject of the present invention are especially compounds of formula I in which one or more substituents or groups, preferably the major part of the substituents or groups has a meaning which is indicated as preferred, more preferred, even more preferred or especially preferred.

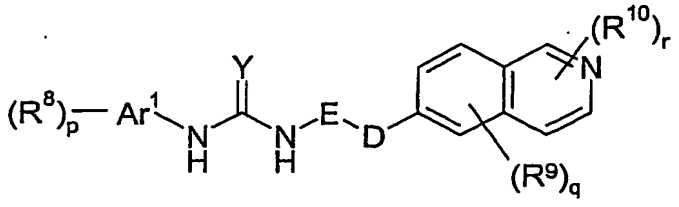
In compounds of formula I, the substituents R^{10} are preferably bound to a carbon atom.

More preferred as compounds of formula I are compounds of formula I',



(I')

and/or compounds of formula I'',



(I")

wherein each residue R^8, p Ar^1, Y, E, D, R^9, R^{10}, q and r are independently selected from the meanings given above/below.

In compounds of formula I, the term alkyl preferably refers to an unbranched or branched alkyl residue, preferably an unbranched alkyl residue comprising 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, preferably 1, 2, 3, 4, 5 or 6, more preferred 1, 2, 3 or 4 and especially 1 or 2 carbon atoms, or a branched alkyl residue comprising 3, 4, 5, 6, 7, 8 ,9 or 10, preferably 3, 4, 5 or 6 more preferred 3 or 4 carbon atoms. The alkyl residues can be optionally substituted, especially by one or more halogen atoms, for example up to perhaloalkyl, by one or more hydroxy groups or by one or more amino groups, all of which can optionally be substituted by alkyl. If an alkyl residue is substituted by halogen, it usually comprises 1, 2, 3, 4 or 5 halogen atoms, depending on the number of carbon atoms of the alkyl residue. For example, a methyl group can comprise, 1, 2 or 3 halogen atoms, an ethyl group (an alkyl residue comprising 2 carbon atoms) can comprise 1, 2, 3, 4 or 5 halogen atoms. If an alkyl residue is substituted by hydroxy groups, it usually comprises one or two, preferably one hydroxy groups. If the hydroxy group is substituted by alkyl, the alkyl substituent comprises preferably 1 to 4 carbon atoms and is preferably unsubstituted or substituted by halogen and more preferred unsubstituted. If an alkyl residue is substituted by amino groups, it usually comprises one or two, preferably one amino groups. If the amino group is substituted by alkyl, the alkyl substituent comprises preferably 1 to 4 carbon atoms and is preferably unsubstituted or substituted by halogen and more preferred unsubstituted. According to compounds of formula I, alkyl is preferably selected from the group consisting of methyl, ethyl, trifluoro methyl, pentafluoro ethyl, isopropyl, tert.-butyl, 2-amino ethyl, N-methyl-2-

amino ethyl, N,N-dimethyl-2-amino ethyl, N-ethyl-2-amino ethyl, N,N-diethyl-2-amino ethyl, 2-hydroxy ethyl, 2-methoxy ethyl and 2-ethoxy ethyl, further preferred of the group consisting of 2-butyl, n-pentyl, neo-nentyl, isopentyl, hexyl and n-decyl, more preferred of methyl, ethyl, trifluoro methyl, isoproply and tert.-butyl.

In compounds of formula I, alkenyl is preferably selected from the group consisting of allyl, 2- or 3-butenyl, isobutenyl, sec-butenyl, furthermore preferably 4-pentenyl, isopentenyl and 5-hexenyl.

In compounds of formula I, alkylene is preferably unbranched and is more preferably methylene or ethylene, furthermore preferably propylene or butylene.

In compounds of formula I, alkylenecycloalkyl preferably has 5 to 10 carbon atoms and is preferably methylenecyclopropyl, methylenencyclobutyl, furthermore preferably methylenecyclopentyl, methylenecyclohexyl or methylenecycloheptyl, furthermore alternatively ethylenecyclopropyl, ethylenecyclobutyl, ethylenecyclopentyl, ethylenecyclohexyl or ethylenencycloheptyl, propylenecyclopentyl, propylenecyclohexyl, butylenecyclopentyl or butylenecyclohexyl.

In compounds of formula I, the term "alkoxy" preferably comprises groups of formula O-alkyl, where alkyl is an alkyl group as defined above. More preferred, alkoxy is selected from group consisting of methoxy, ethoxy, n-propoxy, isopropoxy, 2-butoxy, tert.-butoxy and halogenated, especially perhalogenated, derivatives thereof. Preferred perhalogenated derivatives are selected from the group consisting of O-CCl_3, O-CF_3, O-C_2Cl_5, O-C_2F_5, O-$C(CCl_3)_3$ and O-$C(CF_3)_3$.

In compounds of formula I, the term "alkoxyalkyl" preferably comprises branched and unbranched residues, more preferred unbranched residues, of

formula C_uH_{2u+1}-O-$(CH_2)_v$, wherein u and v are independently from each other 1 to 6. Especially preferred is u = 1 and v 1 to 4.

In compounds of formula I the term "alkoxyalkyl" includes alkoxyalkyl groups as defined above, wherein one or more of the hydrogen atoms are substituted by halogen, for example up to perhalo alkoxyalkyl.

In compounds of formula I, cycloalkyl preferably has 3 – 7 carbon atoms and is preferably cyclopropyl or cyclobutyl, furthermore preferably cyclopentyl or cyclohexyl, furthermore also cycloheptyl, particularly preferably cyclopentyl. The term "cycloalkyl", as used herein preferably also includes saturated heterocyclic groups, wherein one or two carbon atoms are substituted by hetero atoms, selected from the group consisting of O, NH, NA and S, wherein A is as defined as above/below. Cycloalkyl residues as defined herein can optionally be substituted, the substituents preferably selected from A, R^{13}, =O, =S, =N-R^{14}, CN and hal.

In compounds of formula I, Ar^3 to Ar^6 are preferably selected independently from one another from phenyl, naphthyl and biphenyl which is optionally substituted by one or more substituents, selected from the group consisting of A, Hal, NO_2, CN, OR^{15}, $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15}, $SO_2NR^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$.

In compounds of formula I, Het is preferably an optionally substituted aromatic heterocyclic residue and even more preferred an optionally substituted saturated heterocyclic residue. In substituted saturated heterocyclic residues, the substituents are preferably selected from A, R^{13}, =O, =S, =N-R^{14}, CN and hal. Even more preferred, Het is selected from the group consisting of 1-piperidyl, 4-piperidyl, 1-methyl-piperidin-4-yl, 1-piperazyl, 1-(4-methyl)-piperazyl, 4-methylpiperazin-1-yl amine, 1-(4-(2-hydroxyethy))-piperazyl, 4-morpholinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-pyrazolidinyl 1-(2-methyl)-pyrazolidinyl, 1-imidazolidinyl or 1-(3-

methyl)-imidazolidinyl, thiophen-2-yl, thiophen-3-yl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, quinolinyl, isoquinolinyl, 2-pyridazyl, 4-pyridazyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 2-pyrazinyl and 3-pyrazinyl. Further preferred, Het as defined above is optionally substituted by one or more substituents preferably selected from A, R^{13}, =O, =S, =N-R^{14}, CN and hal. More preferred, Het is either unsubstituted or substituted once or twice by =O.

In compounds of formula I, saturated heterocyclyl is preferably a substituted or unsubstituted saturated heterocyclic residue, more preferred an unsubstituted saturated heterocyclic residue, preferably selected from the saturated groups given above in the definition of Het. Further preferred, saturated heterocyclyl as defined above is optionally substituted by one or more substituents preferably selected from A, R^{13}, =O, =S, =N-R^{14}, CN and hal. More preferred, saturated heterocyclyl is either unsubstituted or substituted once or twice by =O.

In compounds of formula I, aromatic hydrocarbons containing 6 to 14 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 10 carbon atoms and one or two heteroatoms, independently selected from N, O and S, are preferably selected from the definitions given herein for aryl, heteroaryl and/or Het. Heteroaryl is more preferably furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, oxo-pyridyl, thiadiazolyl, isothiazolyl, pyridyl, pyridazyl, pyrazinyl, pyrimidyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, indolyl, indazolyl and even more preferably pyridinyl, pyrimidyl, quinolinyl, isoquinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl and/or imidazolyl. Aryl more preferably refers to an optionally substituted benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene rings to form, for example, anthracene, phenanthrene, or napthalene ring

systems. Even more preferably, aryl is selected from the group consisting of phenyl, 2-naphthyl, 1-naphthyl, biphenyl.

In compounds of formula I, Ar^1 is preferably selected from the group consisting of phenyl, pyridinyl, pyrimidyl, quinolinyl, isoquinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl and imidazolyl, and especially from phenyl, pyridinyl, quinolinyl, isoquinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl and oxazolyl. Especially preferred, Ar^1 is phenyl or pyridinyl.

In compounds of formula I, $(CR^5R^6)_n$ and $(CR^5R^6)_k$ preferably form a linear or branched alkylen residue, preferably linear or branched C_1-C_4 alkylen residue, which is optionally substituted as described above/below and preferably is unsubstituted.

In compounds of formula I, A and D preferably both are CR^5R^6, respectively. Accordingly, A and D preferably form a linear or branched alkylen residue, more preferably linear or branched C_1-C_4 alkylen residue, which is optionally substituted as described above/below and preferably is unsubstituted.

Preferably, the sum of h and i in one residue exceeds 0.

Preferably, the sum of n and k in one residue exceeds 0.

Another preferred aspect of the instant invention relates to compounds of formula I, wherein n is 0 in the residues R^8, R^9 and/or R^{10} and especially in R^{10}.

Another preferred aspect of the instant invention relates to compounds of formula I, wherein in the residues R^7, n is 1 or 2 and especially is 2.

The invention relates in particular to compounds of the formula I in which at least one of said radicals has one of the preferred meanings given above.

Some more preferred groups of compounds may be expressed by the following sub-formulae I.1) to I.16), which correspond to the formula I and in which radicals not denoted in greater detail are as defined in the formula I, but in which

I.1)	Ar^1	is phenyl, pyridinyl, pyrimidyl, quinolinyl, isoquinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, quinolinyl, isoquinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl;
I.2)	Ar^1	is phenyl, pyridinyl, pyrimidyl, quinolinyl, isoquinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, quinolinyl, isoquinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl, and
	p	is 1, 2 or 3;
I.3)	Ar^1	is phenyl, pyridinyl, pyrimidyl, quinolinyl, isoquinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, quinolinyl, isoquinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,
	p	is 1, 2 or 3, and

R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^1$ and/or OHet, $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$, $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$;

I.4) Ar^1 is phenyl, pyridinyl, pyrimidyl, quinolinyl, isoquinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, quinolinyl, isoquinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,

p is 1, 2 or 3,

R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$ and/or OHet, $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$,

$N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, wherein

n is 0 or 1;

I.5) Ar^1 is phenyl, pyridinyl, pyrimidyl, quinolinyl, isoquinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, quinolinyl, isoquinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,

p is 1, 2 or 3,

R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$ and/or OHet, $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$, $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, wherein

n is 0 or 1, and

k is 1 or 2;

I.6) Ar^1 is phenyl, pyridinyl, pyrimidyl, quinolinyl, isoquinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, quinolinyl, isoquinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,

p is 1, 2 or 3,

R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$ and/or OHet, $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$, $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, wherein

n is 0 or 1,

k is 1 or 2, and

u is 0;

I.7) Ar^1 is phenyl, pyridinyl, pyrimidyl, quinolinyl, isoquinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, quinolinyl, isoquinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,

p is 1, 2 or 3,

R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$ and/or OHet, $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$, $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, wherein

n is 0 or 1,

k is 1 or 2,

u is 0,

q is 0 or 1, and

R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$;

I.8) Ar^1 is phenyl, pyridinyl, pyrimidyl, quinolinyl, isoquinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, quinolinyl, isoquinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,

p is 1, 2 or 3,

R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$ and/or OHet, $N(R^{11})$Het, $(CR^5R^6)_k$Het, $O(CR^5R^6)_k$Het, $N(R^{11})(CR^5R^6)_k$Het, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$,

$NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, wherein

n is 0 or 1,

k is 1 or 2,

u is 0,

q is 0 or 1, and

R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, wherein

n is 0, 1 or 2, preferably 0 or 1;

I.9) Ar^1 is phenyl, pyridinyl, pyrimidyl, quinolinyl, isoquinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, quinolinyl, isoquinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,

p is 1, 2 or 3,

R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$ and/or OHet, $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$, $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, wherein

n is 0 or 1,

k is 1 or 2,

u is 0,

q is 0 or 1,

R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$,

$(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, wherein

n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

I.10) p is 1, 2 or 3,

R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$ and/or OHet, $N(R^{11})$Het, $(CR^5R^6)_k$Het, $O(CR^5R^6)_k$Het, $N(R^{11})(CR^5R^6)_k$Het, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, wherein

n is 0 or 1,

k is 1 or 2,

u is 0,

q is 0 or 1,

R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, wherein

n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

I.11) R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$ and/or OHet, $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$, $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, wherein

n is 0 or 1,

k is 1 or 2,

u is 0,

q is 0 or 1,

R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, wherein

n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

I.12) R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$,

$(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$ and/or OHet, $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$, $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, wherein

u is 0, and

q is 0 or 1, and

R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, wherein

n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

I.13) R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4

carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$ and/or OHet, $N(R^{11})$Het, $(CR^5R^6)_k$Het, $O(CR^5R^6)_k$Het, $N(R^{11})(CR^5R^6)_k$Het, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, wherein

q is 0 or 1, and

R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, wherein

n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

I.14) q is 0 or 1, and

R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, wherein

n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

I.15) R^{10} is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$,

n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

I.16) R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, and

r is 0, 1 or 2, preferably 0 or 1.

One preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein p is 1, 2 or 3 and R^8 is independently selected from the group consisting of methyl, ethyl, isopropyl, tert.-butyl, F, Cl, Br, CF_3, $C(CF_3)_3$, SO_2CF_3, methoxy, ethoxy, tert.-butoxy, perfluoro tert.-butoxy ($OC(CF_3)_3$), methyl sulfanyl (SCH_3), ethyl sulfanyl (SCH_2CH_3), acetyl ($COCH_3$), propionyl ($COCH_2CH_3$), butyryl ($COCH_2CH_2CH_3$). If p is 2 or 3, all substituents can be the same or different.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein Y is selected from the group consisting of $C(R^{22})$-NO_2, $C(R^{22})$-CN and $C(CN)_2$.

Another more preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein Y is selected from the group consisting of O, S and NR^{21}.

Another even more preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein Y is selected from the group consisting of O and S.

Another even more preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein Y is O.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein r is either 0 or 1. If r is 1, R^{10} is preferably $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, wherein n in 0. In this embodiment, R^{11} is preferably selected from the group consisting of H and A and more preferred from H and alkyl, and R^{12} is preferably selected from the group consisting of H and A and more preferred from H and alkyl. Especially preferred as residue R^{10} are carbamoyl, more preferred alkyl carbamoyl or dialkyl carbamoyl, even more preferred methyl carbamoyl or dimethyl carbamoyl, ethyl carbamoyl or diethyl carbamoyl and especially preferred methyl carbamoyl (-$CONHCH_3$). Preferably, R^{10} is bonded in a vicinal position to the nitrogen atom of the isoquinoline residue, i.e. in 2- and/or 6-position of the isoquinoline residue.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein Ar^1 is phenyl.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein Ar^1 comprises two or more substituents R^8, wherein one or more, preferably

one substituent R^8 is selected from the group consisting of $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{12}R^{12}$, $(CH_2)_nCOOR^{13}$ and $(CH_2)_nS(O)_uR^{13}$ wherein R^{11}, R^{12} and R^{13} are defined as above and n is as defined above, preferably n is 0, 1 or 2 and especially is 0, k is 1 to 4 and preferably 1 or 2, and u is preferably 2. In this embodiment R^{11}, R^{12} and R^{13} are more preferably selected independently from each other from the group consisting of H, methyl and ethyl. In this embodiment, one or two substituents R^8 and preferably one substituent R^8 is especially preferably selected from the group consisting of NH_2, $N(CH_3)_2$, $N(C_2H_5)_2$, $NHCH_2CH_2NH_2$, $N(CH_3)CH_2CH_2NH_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2OCH_3$, $OCH_2CH_2N(CH_3)_2$, SCH_3, SC_2H_5, SO_2CH_3, $COOCH_3$ and COOH. Accordingly, in this embodiment Ar^1 especially preferably comprises at least one substituent R^8 other than $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{12}R^{12}$, $(CH_2)_nCOOR^{13}$ and $(CH_2)_nS(O)_uR^{13}$ as defined in this paragraph and especially other than NH_2, $N(CH_3)_2$, $N(C_2H_5)_2$, $NHCH_2CH_2NH_2$, $N(CH_3)CH_2CH_2NH_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2OCH_3$, $OCH_2CH_2N(CH_3)_2$, SCH_3, SC_2H_5, SO_2CH_3, $COOCH_3$ and COOH.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein Ar^1 comprises two or more substituents R^8, wherein one or more, preferably one substituent R^8 is selected from the group consisting of OHet, $N(R^{11})$Het, $(CR^5R^6)_k$Het, $O(CR^5R^6)_k$Het, $N(R^{11})(CR^5R^6)_k$Het, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$ and $NR^{11}(CR^5R^6)_kOR^{13}$, wherein R^{11}, R^{12}, R^{13} and Het are defined as above/below and n is as defined above, preferably n is 0, 1 or 2 and especially is 0, k is 1 to 4 and preferably 1 or 2. In this embodiment R^{11}, R^{12} and R^{13} are more preferably selected independently from each other from the group consisting of H, methyl and ethyl. In this embodiment, one or two substituents R^8 and preferably one

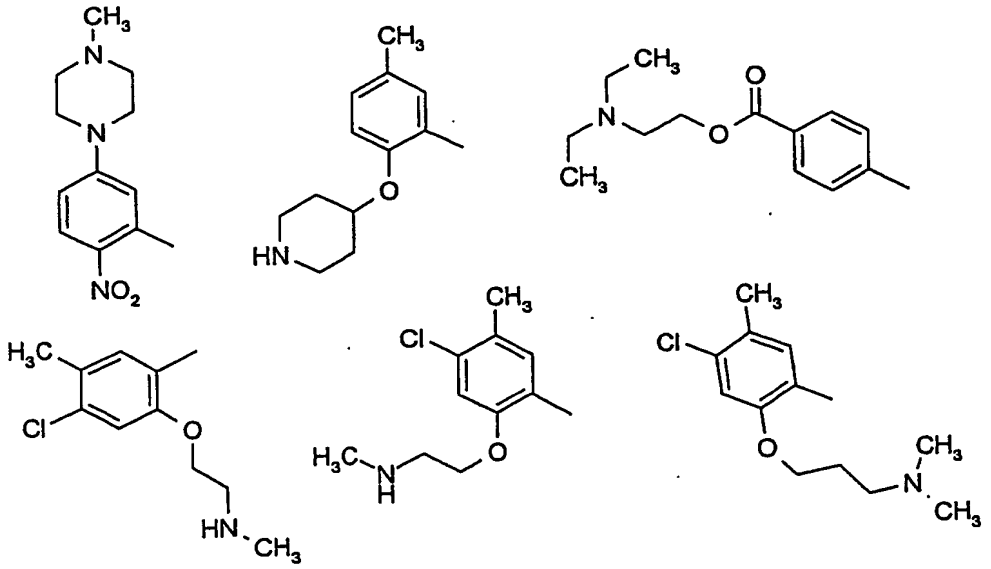
substituent R^8 is especially preferably selected from the group consisting of OHet, OCH_2CH_2Het, $NHCH_2CH_2NH_2$, $OCH_2CH_2NH_2$, $NHCH_2C(CH_3)NH_2$, $OCH_2C(CH_3)NH_2$, $NHC(CH_3)CH_2NH_2$, $OC(CH_3)CH_2NH_2$, $N(CH_3)CH_2CH_2NH_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2OCH_3$, $OCH_2CH_2N(CH_3)_2$ and $N(CH_3)CH_2CH_2OCH_3$. Accordingly, in this embodiment Ar^1 especially preferably comprises at least one substituent R^8 other than OHet, $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$, $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$ and $NR^{11}(CR^5R^6)_kOR^{13}$as defined in this paragraph and especially other than OHet, OCH_2CH_2Het, $NHCH_2CH_2NH_2$, $OCH_2CH_2NH_2$, $NHCH_2C(CH_3)NH_2$, $OCH_2C(CH_3)NH_2$, $NHC(CH_3)CH_2NH_2$, $OC(CH_3)CH_2NH_2$, $N(CH_3)CH_2CH_2NH_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2OCH_3$, $OCH_2CH_2N(CH_3)_2$ and $N(CH_3)CH_2CH_2OCH_3$.

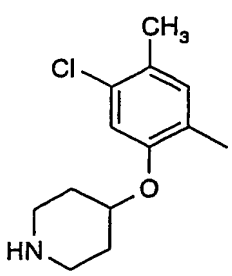
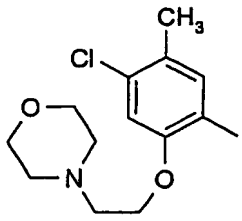
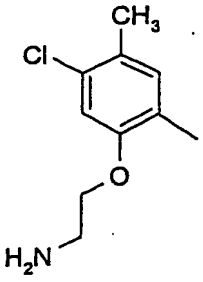
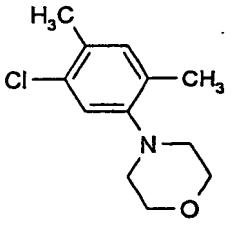
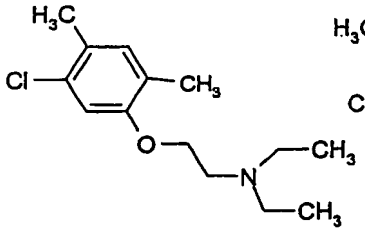
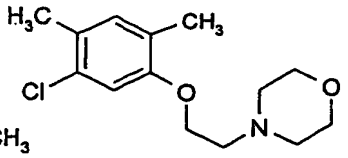
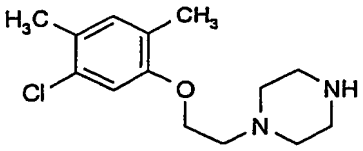
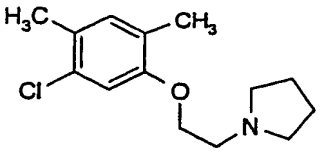
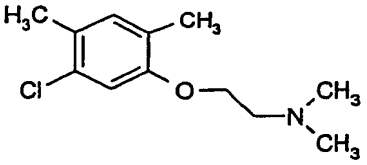
Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of formulae I.1) to I.16), wherein $(R^8)_p$-Ar^1 is selected from the group consisting of 3-acetyl-phenyl, 4-acetyl-phenyl, 2-bromo-phenyl, 3-bromo-phenyl, 4-bromo-phenyl, 4-bromo-2-chloro-phenyl, 4-bromo-3-methyl-phenyl, 4-bromo-3-trifluoromethyl-phenyl, 2-chloro-phenyl, 2-chloro-4-trifluoromethyl-phenyl, 2-chloro-5-trifluoromethyl-phenyl, 3-chloro-phenyl, 3-chloro-4-methyl-phenyl, 3-chloro-4-methoxy-phenyl, 3-chloro-4-methoxy-phenyl, 4-chloro-phenyl, 4-chloro-2-trifluoromethyl-phenyl, 4-chloro-3-trifluoromethyl-phenyl, 4-chloro-2-methyl-phenyl, 5-chloro-2-methyl-phenyl, 5-chloro-2-methoxy-phenyl, 2,3-dichloro-phenyl, 2,4-dichloro-phenyl, 2,5-dichloro-phenyl, 3,4-dichloro-phenyl, 3,5-dichloro-phenyl, 2,4,5-trichloro-phenyl, 4-fluoro-phenyl, 4-fluoro-3-trifluoromethyl-phenyl, 4-ethoxy-phenyl, 2-methoxy-phenyl, 2-methoxy-5-trifluoromethyl-phenyl, 4-methoxy-phenyl, 2,5-dimethoxy-phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 3-trifluoromethoxy-phenyl, 4-trifluoromethyl-phenyl, 4-trifluoromethoxy-phenyl, 3,5-bis-trifluoromethyl-phenyl, 3-methoxy-phenyl, 3-methylsulfanyl-phenyl, 4-methylsulfanyl-phenyl, o-tolyl (2-methyl-phenyl), m-

tolyl (3-methyl-phenyl), p-tolyl (4-methyl-phenyl), 2,3-dimethyl-phenyl, 2,3-dimethyl-phenyl, 2,5-dimethyl-phenyl, 3,4-dimethyl-phenyl, 3,5-dimethyl-phenyl, 2-ethyl-phenyl, 3-ethyl-phenyl, 4-ethyl-phenyl, 4-isopropyl-phenyl, 4-tert-butyl-phenyl and 5-tert-butyl-isoxazol-3-yl; and/or 5-chloro-2-methoxy-4-methyl-phenyl and 4-chloro-2-methoxy-5-trifluoromethyl-phenyl. Additionally preferred are compounds of formula I and preferably one or more of formulae I.1) to I.16), wherein $(R^8)_p$-Ar^1 is selected from the the residues given above, that additionally comprise one or two, preferably one additional substituent $(R^8)_p$ and especially one or two, preferably one additional substituent $(R^8)_p$ indicated herein as preferred, more preferred or especially preferred.

Another preferred embodiment of the instant invention relates to compounds of formula I and the subformulae related thereto and preferably one or more of formulae I.1) to I.16), wherein the residues $(R^8)_p$-Ar^1 are selected from the group consisting of the following formulae:

a)



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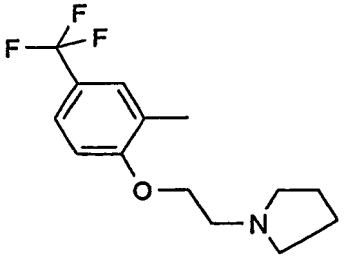
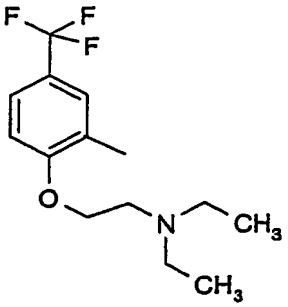
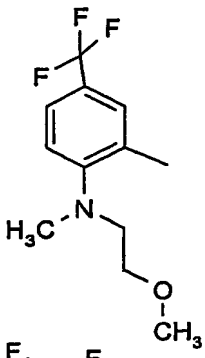
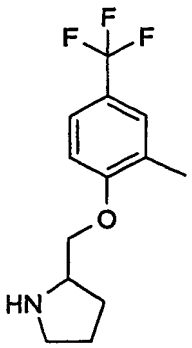
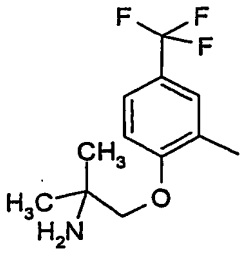
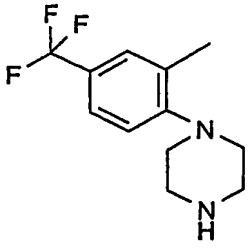
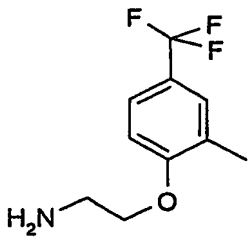

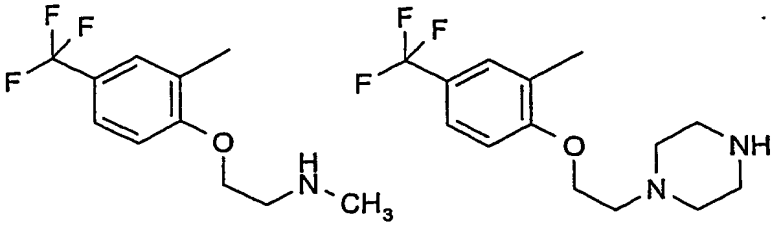

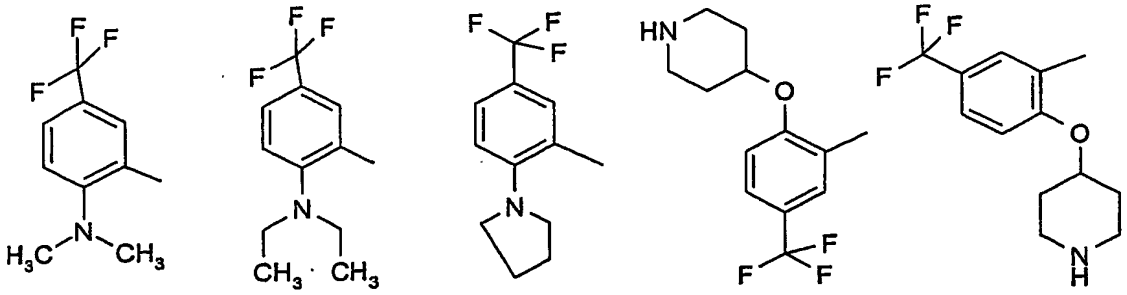

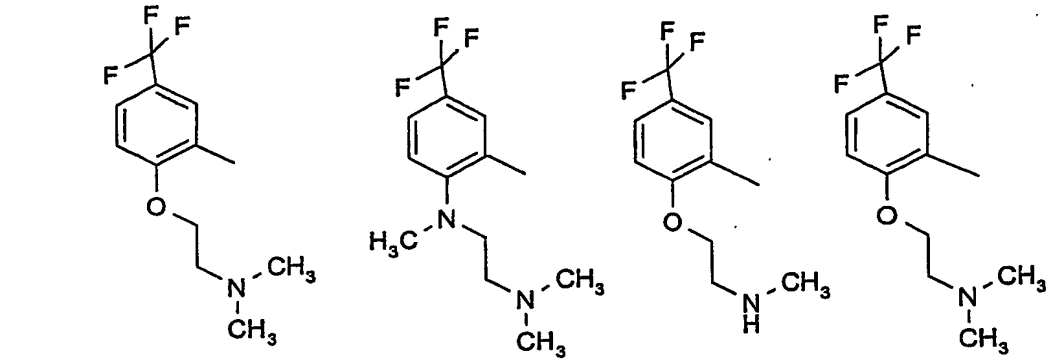

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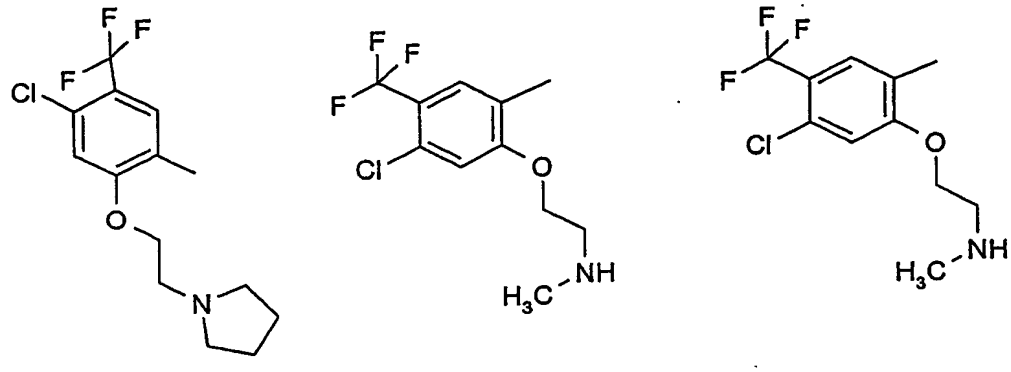

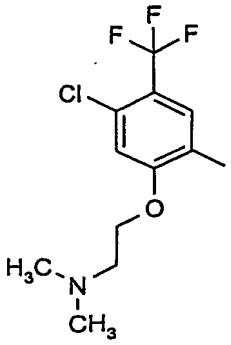
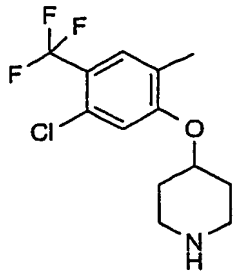
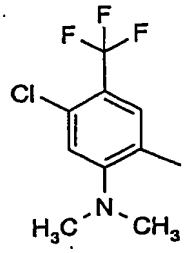
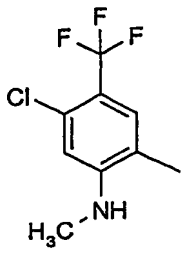

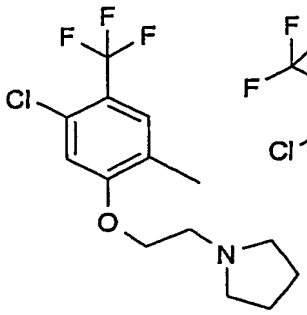
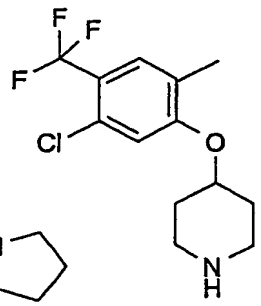
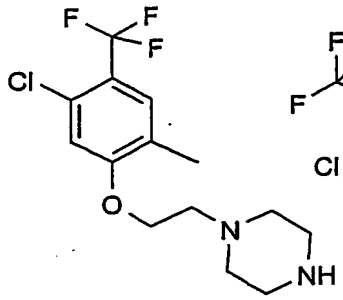
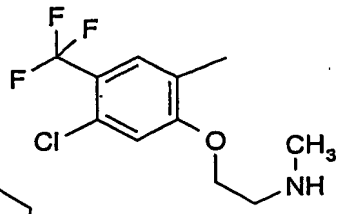

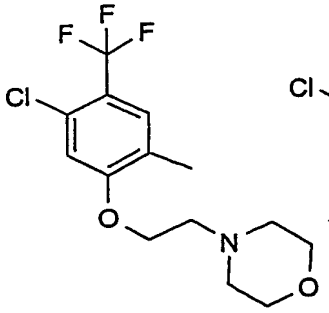
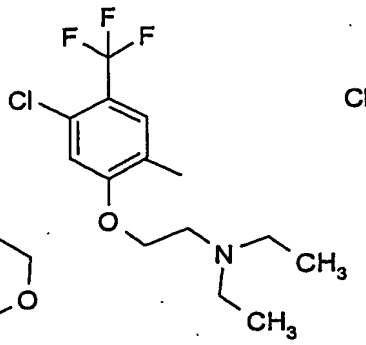
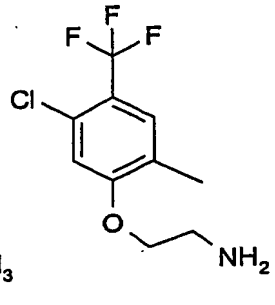

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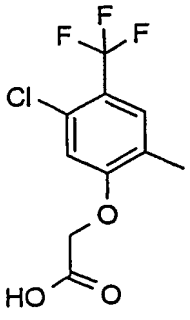
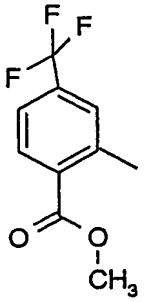
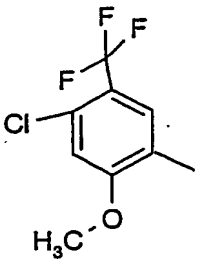
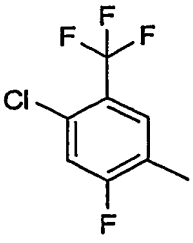

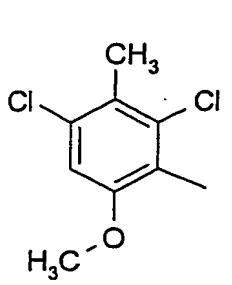

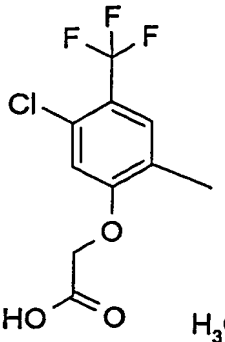

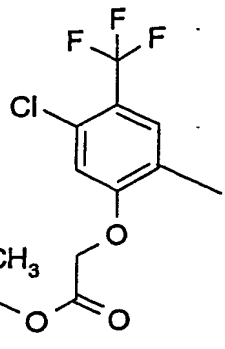

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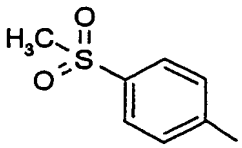

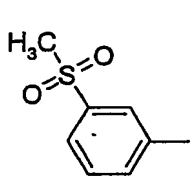

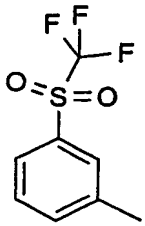

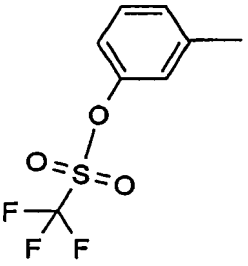

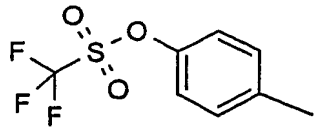

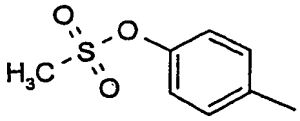

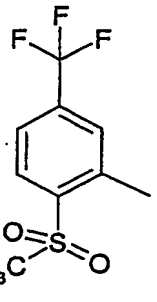

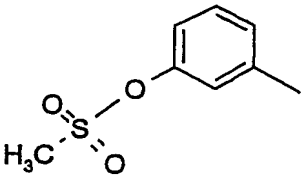

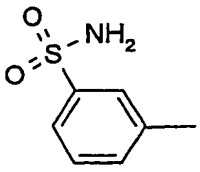

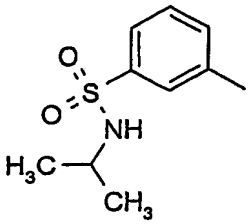

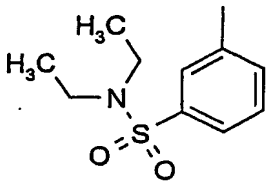

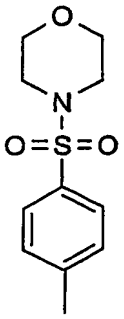

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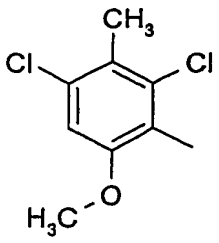
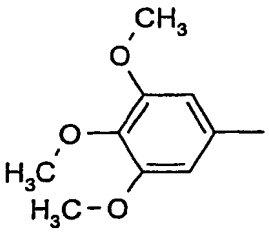

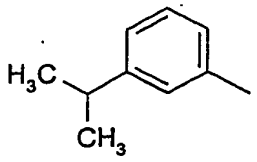
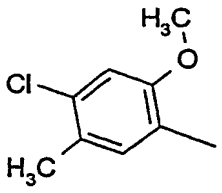
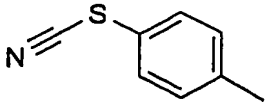

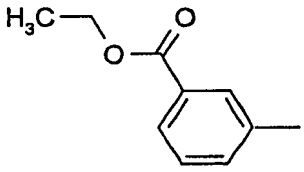
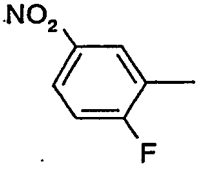
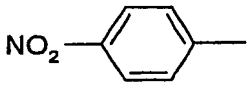

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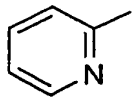
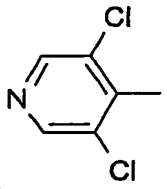
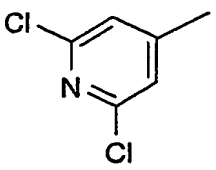
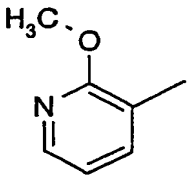

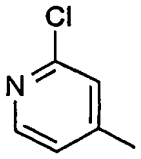
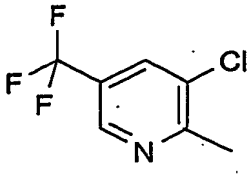
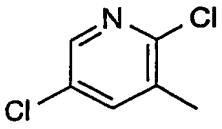

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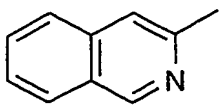
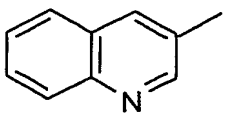
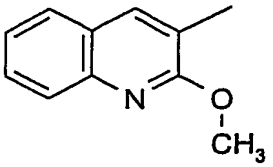

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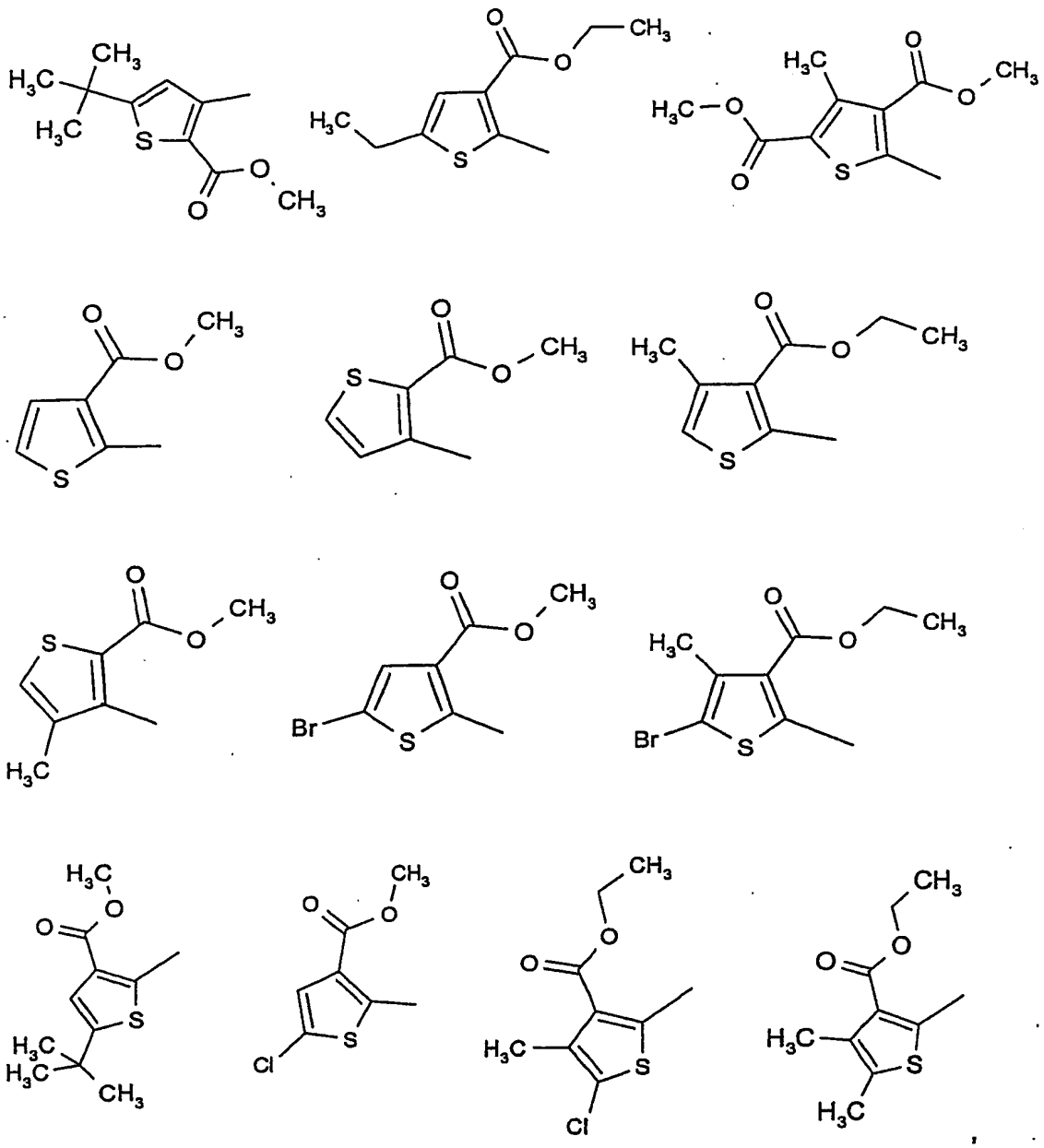


and/or residues of the structures given above that comprise one or two, preferably one additional substituent, independently selected from the meanings given for R^8.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein $(R^8)_p$-Ar^1 is as defined above, but comprises one or more additional residues,

preferably one additional residue. The additional residues are preferably selected from the meanings given for R^8 and more preferably selected from the group consisting of $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nS(O)_uNR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$ wherein R^{11}, R^{12} and R^{13} are defined as above and n is as defined above, preferably n is 0, 1 or 2 and especially is 0, k is 1 to 4 and preferably 1 or 2, and u is preferably 2. In this embodiment R^{11}, R^{12} and R^{13} are more preferably selected independently from each other from the group consisting of H, methyl and ethyl. Even more preferred, the additional residue(s) is/are selected from the group consisting of NH_2, $N(CH_3)_2$, $N(C_2H_5)_2$, $NHCH_2CH_2NH_2$, $N(CH_3)CH_2CH_2NH_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2OCH_3$, $OCH_2CH_2N(CH_3)_2$, SCH_3, SC_2H_5, SO_2CH_3, SO_2CF_3, OSO_2CH_3, OSO_2CF_3, SO_2NH_2, $SO_2NHCH(CH_3)_2$, $SO_2N(CH_3)_2$, $SO_2N(CH_2CH_3)_2$, 4-Morpholine-4-sulfonyl, $COOCH_3$ and COOH.

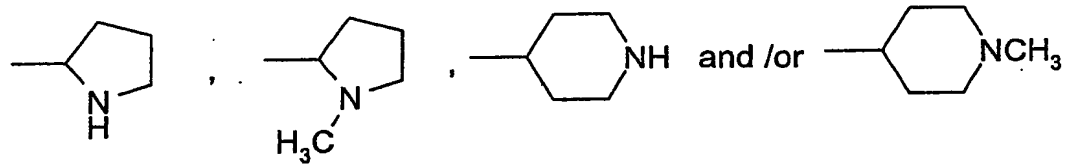
Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein $(R^8)_p$-Ar^1 is as defined above, but comprises one or more additional residues, preferably one additional residue. The additional residues are preferably selected from the meanings given for R^8 and more preferably selected from the group consisting of OHet, $N(R^{11})$Het, $(CR^5R^6)_k$Het, $O(CR^5R^6)_k$Het, $N(R^{11})(CR^5R^6)_k$Het, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$ and $NR^{11}(CR^5R^6)_kOR^{13}$, wherein R^{11}, R^{12}, R^{13} and Het are defined as above/below and n is as defined above, preferably n is 0, 1 or 2 and especially is 0, k is 1 to 4 and preferably 1 or 2. In this embodiment R^{11}, R^{12} and R^{13} are more preferably selected independently from each other from the group consisting of H, methyl and ethyl. Even more preferred, the additional residue(s) is/are selected from the group consisting of OHet, OCH_2CH_2Het, $NHCH_2CH_2NH_2$, $OCH_2CH_2NH_2$, $NHCH_2C(CH_3)NH_2$, $OCH_2C(CH_3)NH_2$, $NHC(CH_3)CH_2NH_2$, $OC(CH_3)CH_2NH_2$, $N(CH_3)CH_2CH_2NH_2$,

$N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2OCH_3$, $OCH_2CH_2N(CH_3)_2$ and $N(CH_3)CH_2CH_2OCH_3$

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein Ar^1 comprises two or more substituents R^8, wherein one or more, preferably one substituent R^8 comprises a group $NR^{11}R^{12}$, wherein R^{11} and R^{12} form, together with the N-atom they are bound to, a 5-, 6- or 7- membered heterocyclus which optionally contains 1 or 2 additional hetero atoms, selected from N, O and S, which optionally is substituted by one or more substituent, selected from A, R^{13}, =O, =S and =N-R^{14}. In this embodiment, the heterocyclus is preferably selected from morpholine, piperazine, piperidne, pyrrolidine, especially from 1-piperidyl, 4-piperidyl, 1-methyl-piperidin-4-yl, 1-piperazyl, 1-(4-methyl)-piperazyl, 4-methylpiperazin-1-yl amine, 1-(4-(2-hydroxyethy))-piperazyl, 4-morpholinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, and/or oxomorpholine, oxopiperazine, oxopiperidine and oxopyrrolidine. More preferably, the oxo substituted heterocyclus is selected from 2-oxo-piperidin-1-yl, 2-oxo-piperidin-4-yl, 1-methyl-2-oxo-piperidin-4-yl, 2-oxo-piperazin-1-yl, 4-methyl-2-oxo-piperazin-1-yl, 4-methyl-2-oxo-piperazin-1-yl amine, 4-(2-hydroxyethy)-2-oxo-piperazin-1-yl, 3-oxo-morpholin-4-yl, 2-oxo-pyrrolidin-1-yl, 2-oxo-pyrrolidin-5-yl and/or 3-oxo-piperidin-1-yl, 3-oxo-piperidin-4-yl, 1-methyl-3-oxo-piperidin-4-yl, 3-oxo-piperazin-1-yl, 4-methyl-3-oxo-piperazin-1-yl, 4-methyl-3-oxo-piperazin-1-yl amine, 4-(2-hydroxyethy)-3-oxo-piperazin-1-yl, 2-oxo-morpholin-4-yl, 3-oxo-pyrrolidin-1-yl, 4-oxo-pyrrolidin-3-yl.

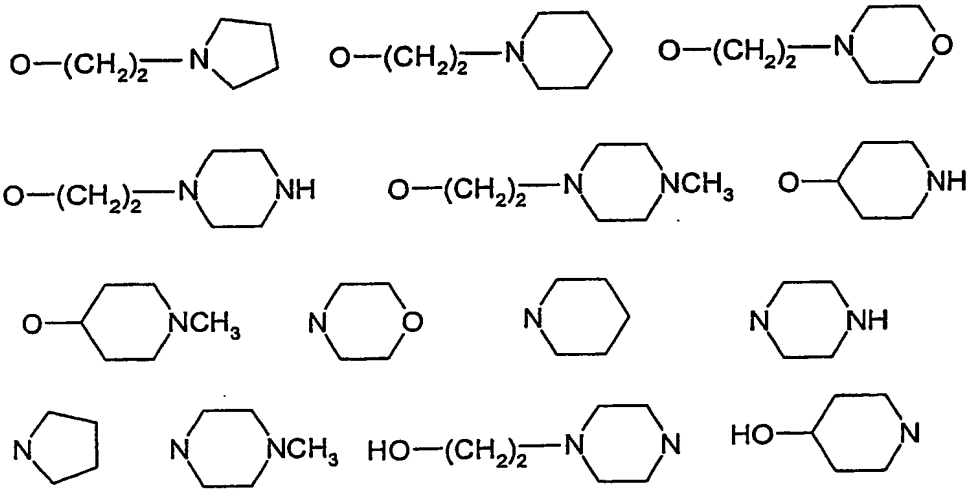
Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein Ar^1 comprises two or more substituents R^8, wherein one or more, preferably one substituent R^8 comprises a terminal group R^{11}, R^{12}, R^{13} or R^{14}, preferably a group R^{13}, that is selected from cycloalkyl and Het, more preferred from cycloalkyl and saturated heterocyclyl and especially from

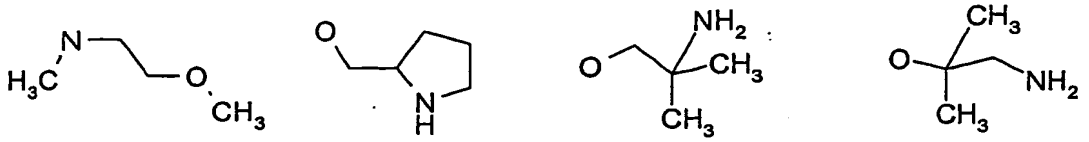
saturated heterocyclyl. In this embodiment, saturated heterocycl is preferably selected from 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-methyl-piperidin-4-yl, 1-methyl-piperidin-3-yl, 1-methyl-piperidin-2-yl, 2-piperazyl, 3-piperazyl, 2-(4-methyl)-piperazyl, 3-(4-methyl)-piperazyl, 4-methylpiperazin-2-yl amine, 4-methylpiperazin-3-yl amine, 2-(4-(2-hydroxyethy))-piperazyl, 3-(4-(2-hydroxyethy))-piperazyl, 3-morpholinyl, 2-morpholinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, and and especially from



Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein Ar^1 comprises two or more substituents R^8 as defined above/below; wherein one or two, preferably one substituent R^8 is selected from the group consisting of residues of formulae aa):

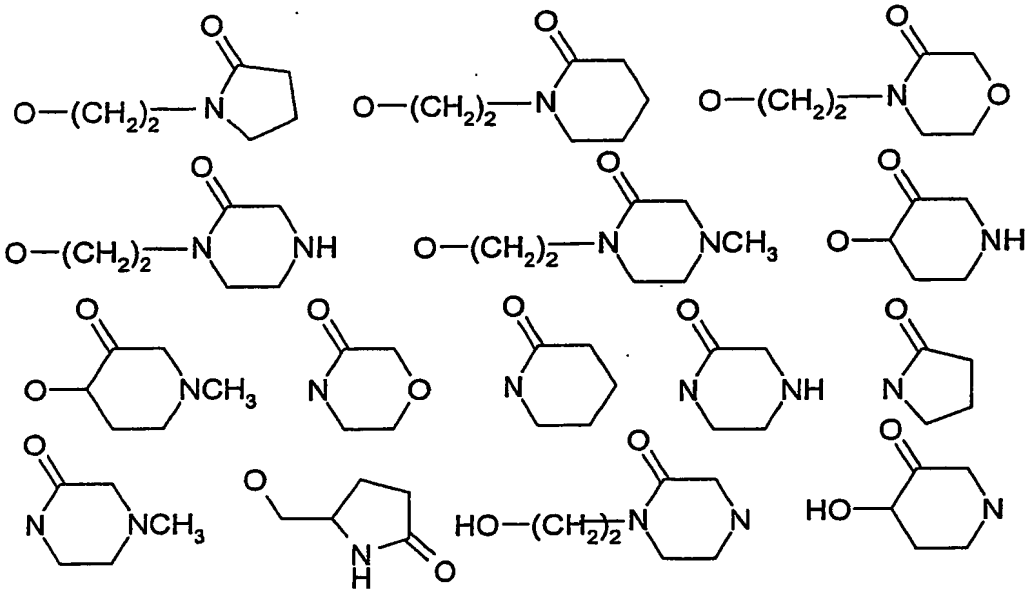
aa)





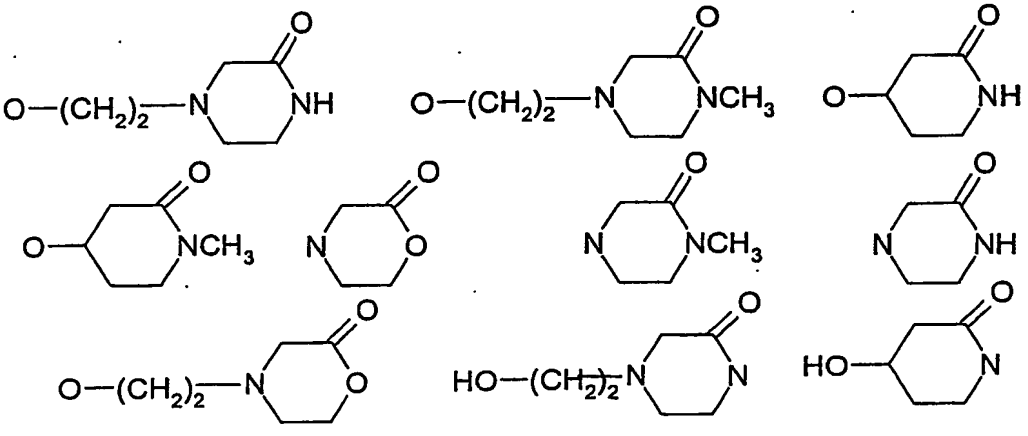
and/or bb):

bb)



and/or cc):

cc)



Another especially preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to

I.16), wherein Ar^1 comprises one or two, preferably one substituent R^8 that is selected from the group consisting of the formulae aa).

Another especially preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein Ar^1 comprises two or more substituents R^8, wherein one or two, preferably one substituent R^8 is selected from the group consisting of the formulae bb).

Another especially preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein Ar^1 comprises two or more substituents R^8, wherein one or two, preferably one substituent R^8 is selected from the group consisting of the formulae cc).

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein Ar^1 comprises two or more substituents R^8, wherein one or two, preferably one substituent R^8 is selected from the group consisting of SO_2CH_3, SO_2CF_3, OSO_2CH_3, OSO_2CF_3, SO_2NH_2, $SO_2NHCH(CH_3)_2$, $SO_2N(CH_3)_2$, $SO_2N(CH_2CH_3)_2$ and 4-Morpholine-4-sulfonyl.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein the isoquinoline residue comprises one or more substituents R^{10} and wherein one or two, preferably one substituent R^{10} is selected from unsubstituted or substituted carbamoyl moieties. Substituted carbamoyl moieties are preferably selected from $CONHR^{23}$ or $CONR^{23}R^{24}$, preferably $CONHR^{23}$, wherein R^{23} and R^{24} are independently selected from the definitions given for R^8, more preferably selected from alkyl, preferably methyl, ethyl, propyl and butyl, $(CH_2)_nNR^{11}R^{12}$ and $(CH_2)_nOR^{12}$, wherein R^{11}, R^{12} and n are as defined above. In this embodiment, n is preferably not 0 and more preferred 1 to 3

and especially 1 or 2. Preferred examples for R^{23} are selected from the group consisting of methyl, ethyl, $CH_2CH_2NH_2$, $CH_2CH_2N(CH_3)_2$, $CH_2CH_2N(CH_2CH_3)_2$, CH_2CH_2OH, $CH_2CH_2OCH_3$ and $CH_2CH_2OCH_2CH_3$.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein the isoquinoline residue comprises one or more substituents R^{10} and wherein one or two, preferably one substituent R^{10} is selected from substituted carbamoyl moieties. Substituted carbamoyl moieties are preferably selected from $CONHR^{23}$, wherein R^{23} is preferably unsubstituted C_1-C_4-alkyl and especially is methyl.

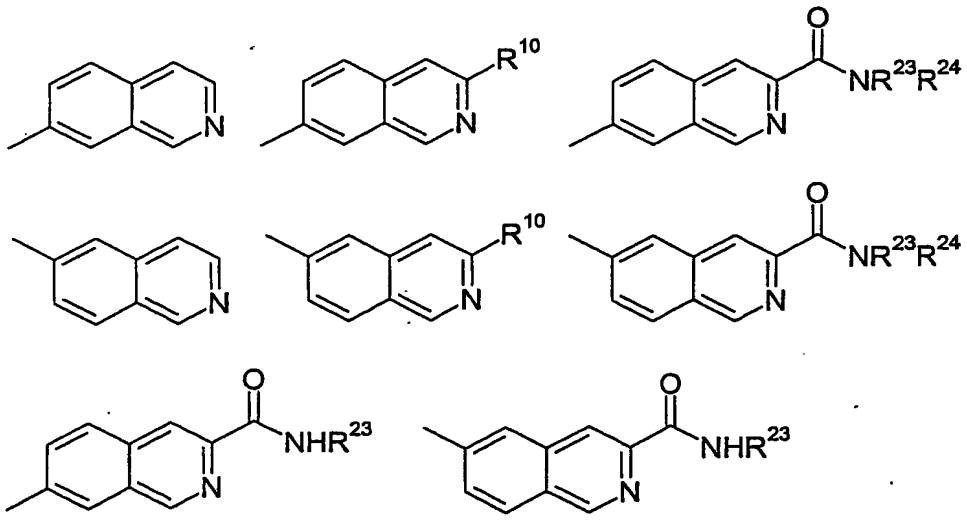
Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein the isoquinoline residue comprises one or more substituents R^{10} and wherein one or two, preferably one substituent R^{10} is selected from substituted carbamoyl moieties. Substituted carbamoyl moieties are preferably selected from $CONHR^{23}$, wherein R^{23} is selected from $(CH_2)_nNR^{11}R^{12}$ and $(CH_2)_nOR^{12}$, wherein R^{11}, R^{12} and n are as defined above. In this embodiment, n is preferably not 0 and more preferred 1 to 3 and especially 1 or 2. Preferred examples for R^{23} are selected from the group consisting of $CH_2CH_2NH_2$, $CH_2CH_2N(CH_3)_2$, $CH_2CH_2N(CH_2CH_3)_2$, CH_2CH_2OH, $CH_2CH_2OCH_3$ and $CH_2CH_2OCH_2CH_3$.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein q is 0, i.e. the 6-membered carbocylic substrucure of the isoquinoline moiety is unsubstituted.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein q is 1 or 2, i.e. the 6-membered carbocylic substrucure of the isoquinoline

moiety is substituted by one or two substituents R^9 as defined above, preferably one or two substituentss elected independently from one another from alkyl and hal, and more preferably selected from CH_3, CH_2CH_3 and hal. and/or residues of the structures given above that comprise one or two, preferably one additional substituent, independently selected from the meanings given for R^8.

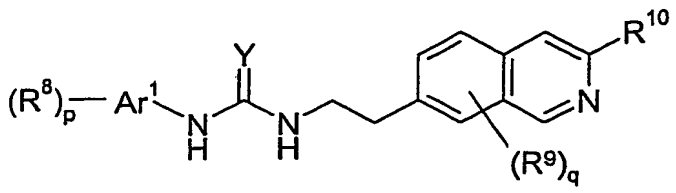
Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein the isoquinoline moiety, which is optionally substituted by one or more substituents R^9 and/or R^{10}, is selected from the structures given below,



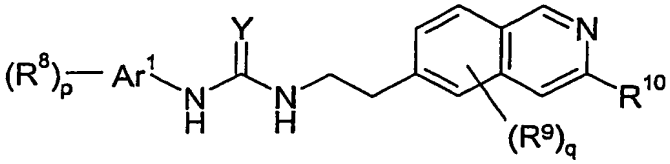
wherein R^{10}, R^{23} and R^{24} are as defined above and below.

Another especially preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16), wherein one or more features of the above and below mentioned embodiments are combined in one compound.

Subject of the present invention are therefore preferably compounds of formula I according to one or both of the formulae Ia and Ib,



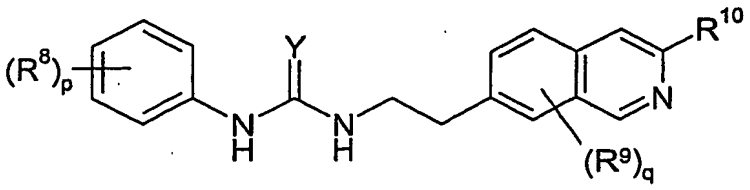
Ia



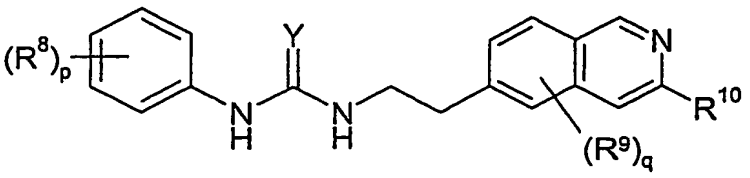
Ib

wherein Ar^1, R^7, R^8, p, g, Y, X, R^9, q, Ar^2, R^{10} and r are as defined above and below, and preferably as defined in sub formulae I.1) to I.16) and/or the embodiments related thereto, and the pharmaceutically acceptable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios, and more preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

Subject of the present invention are therefore especially preferred compounds of formula I according to one or both of the formulae Ic and Id,



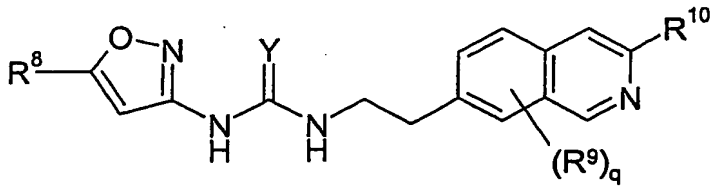
Ic



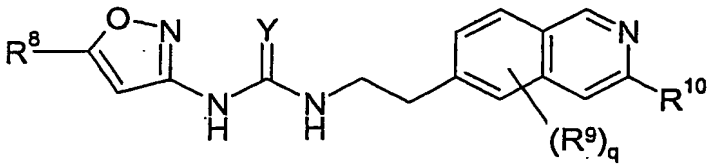
Id

wherein Ar^1, R^8, p, Y, X, R^9 and q are as defined above and below, R^{10} is H or as defined above/below, and preferably as defined in sub formulae I.1) to I.16) and/or the embodiments related thereto;

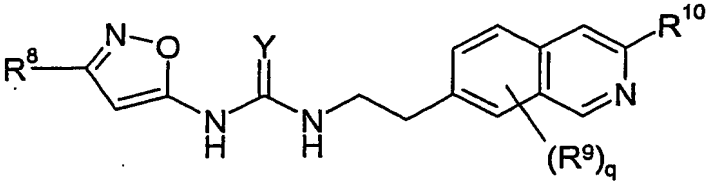
and/or compounds of formula I according to one or more of the formulae Ie to Ir,



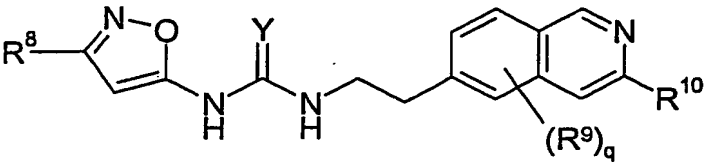
Ie



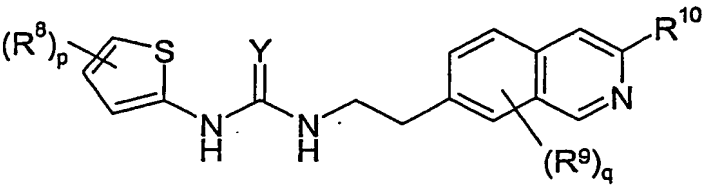
If



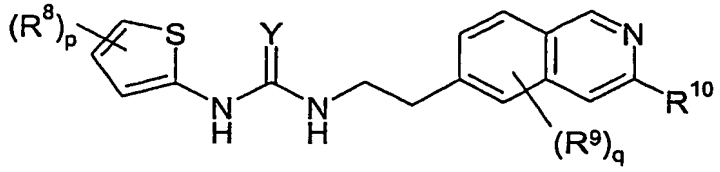
Ig



Ih



Ii



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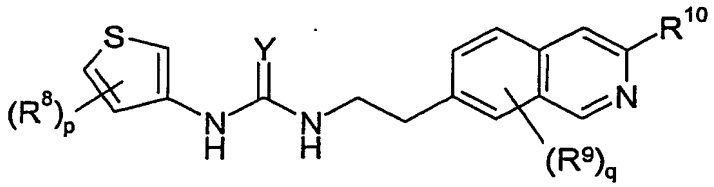
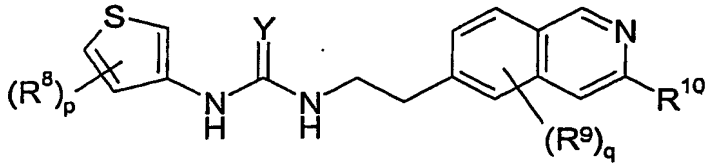
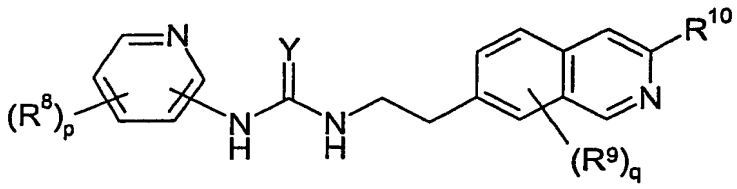


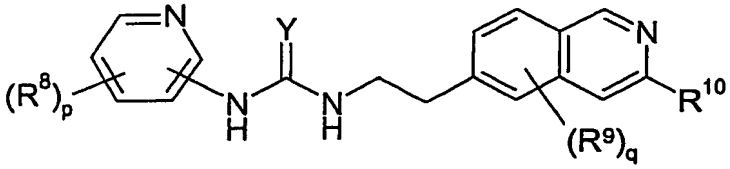
Ik



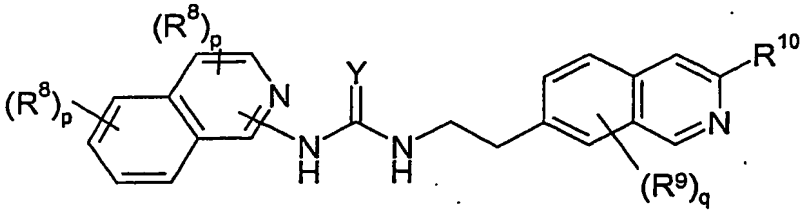
IL



Im



In



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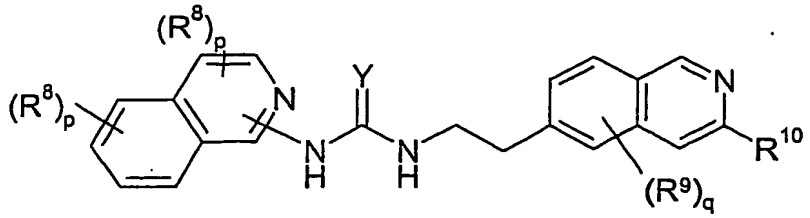
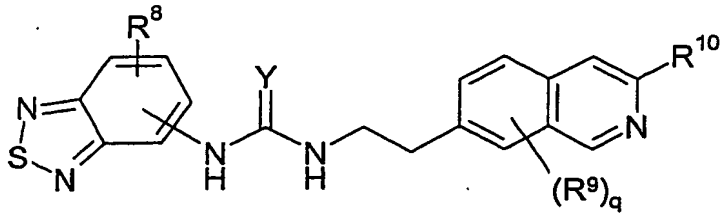
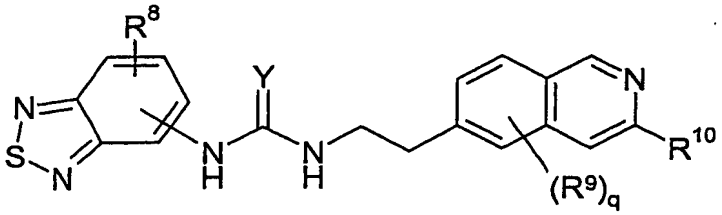


Ip



Iq



Ir

wherein R^8, p, Y, R^9 and q are as defined above and below, R^{10} is H or as defined above/below, and preferably as defined in sub formulae I.1) to I.16) and/or the embodiments related thereto,and the pharmaceutically acceptable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios, and more preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16) and Ia to Ir, wherein R^{10} is a substituted carbamoyl moiety $CONHR^{23}$ or $CONR^{23}R^{24}$, preferably $CONHR^{23}$, wherein R^{23} and R^{24} are independently selected from the definitions given for R^8, more preferably selected from $(CH_2)_nNR^{11}R^{12}$ and $(CH_2)_nOR^{12}$, wherein R^{11}, R^{12} and n are as defined above. In this embodiment, n is preferably not 0 and more preferred 1 to 3 and especially 1

or 2. Preferred examples for R^{23} are selected from the group consisting of $CH_2CH_2NH_2$, $CH_2CH_2N(CH_3)_2$, $CH_2CH_2N(CH_2CH_3)_2$, CH_2CH_2OH, $CH_2CH_2OCH_3$ and $CH_2CH_2OCH_2CH_3$.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16) and Ia to Ir, wherein R^{10} is a substituted carbamoyl moiety $CONHCH_3$.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16) and Ia to Ir, wherein one or more of the substituents R^9 is a C_1-C_4 alkyl residue, preferably an unsubstituted C_1-C_4 alkyl residue, more preferably an unsubstituted alkyl residue selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sek.-butyl and tert.-butyl, more preferably selected from methyl and ethyl, and wherein q is 1, 2, or 3, more preferably 1 or 2.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.16) and Ia to Ir, wherein one or more of the substituents R^9 is selected from hal, preferably from F, Cl, Br and I and more preferably from F, Cl and Br.

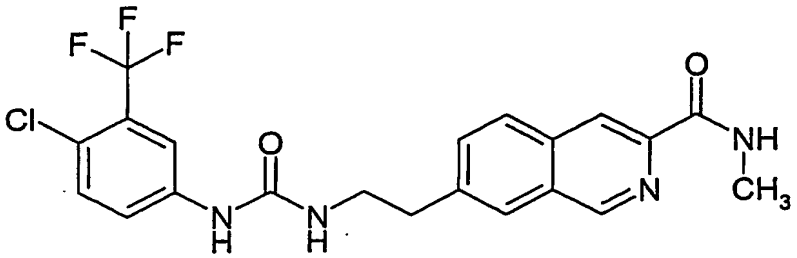
It is understood that when a residue, for example R^8, R^9, R^{10} or R^{14} or R^{23}, is comprised twice or more times in one or more of the formulae I and the sub formulae corresponding thereto, it is in each case independently from one another selected from the meanings given for the respective residue. For example, R^{11} and R^{12} are defined to be independently selected from a group consisting of H, A, $(CH_2)_mAr^3$ and $(CH_2)_mHet$. Then $(CH_2)_nNR^{11}(CH_2)_mNR^{12}R^{12}$ can be $(CH_2)_nNA(CH_2)_mNA_2$ (if R^{11} = A, R^{12} = A and R^{12} = H) as well as $(CH_2)_nNA(CH_2)_mNHA$ (if R^{11} = A, R^{12} = H and R^{12} = A or $(CH_2)_nNA(CH_2)_mNH(CH_{2m}Het$ (if R^{11} = A, R^{12} = H and R^{12} = $(CH_2)_mHet$). Accordingly, if a compound of formula I comprises one residue R^8, R^9 and R^{10}, then for example R^8, R^9 and R^{10} can all be $(CH_2)_nCOOR^{13}$, wherein all

residues R^{13} are the same (for example CH_2Hal, wherein Hal is Cl; then all residues R^8, R^9 and R^{10} are the same) or different (for example CH_2Hal, wherein in R^8 Hal is Cl; in R^9 Hal is F; and in R^{10} Hal is Br; then all residues R^8, R^9 and R^{10} are different); or for example R^8 is $(CH_2)_nCOOR^{13}$, R^9 is NO_2 and R^{10} is $(CH_2)_nSR^{11}$, wherein R^{11} and R^{13} can be the same (for example both can be H or both can be A which is methyl) of different (for example R^{11} can be H and R^{13} can be A which is methyl).

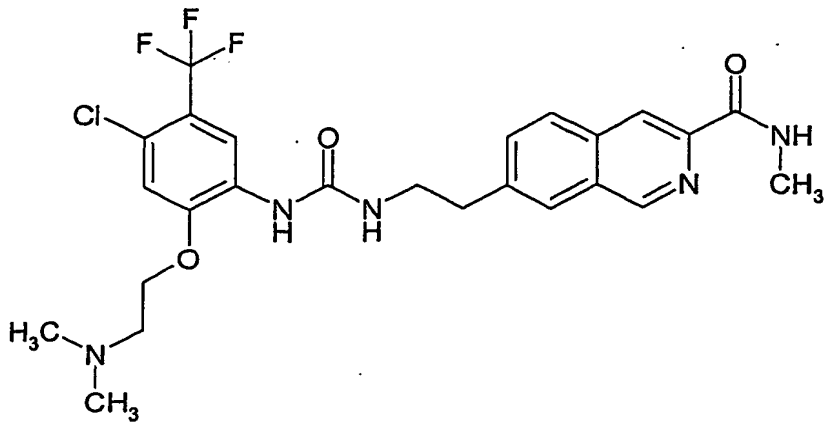
If not stated otherwise, reference to compounds of formula I and formula I also includes the sub formulae related thereto, especially sub formulae I.1) to I.16) and Ia to Ir.

Subject of the instant invention are especially those compounds of formula I and/or formula I, in which at least one of the residues mentioned in said formulae has one of the preferred or especially preferred meanings given above and below.

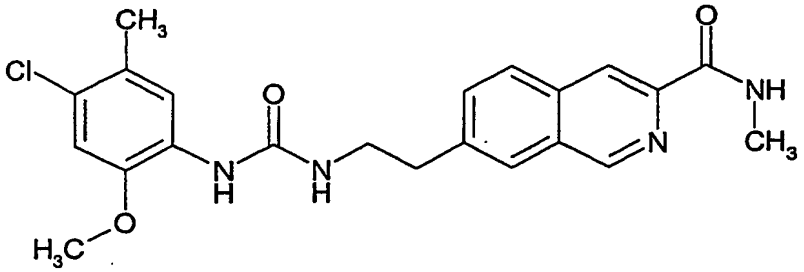
Especially preferred as compounds according to the invention are the compounds given below:



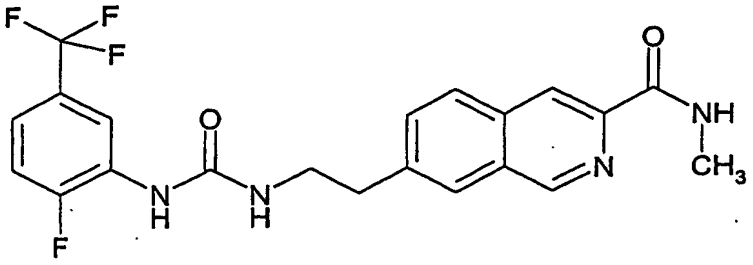
7-{2-[3-(Chloro-trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide (MW = 450.85; Rt = 2.59)



7-(2-{3-[Chloro-(2-dimethylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-ethyl)-isoquinoline-3-carboxylic acid methylamide (MW = 537.97; Rt = 2.02)



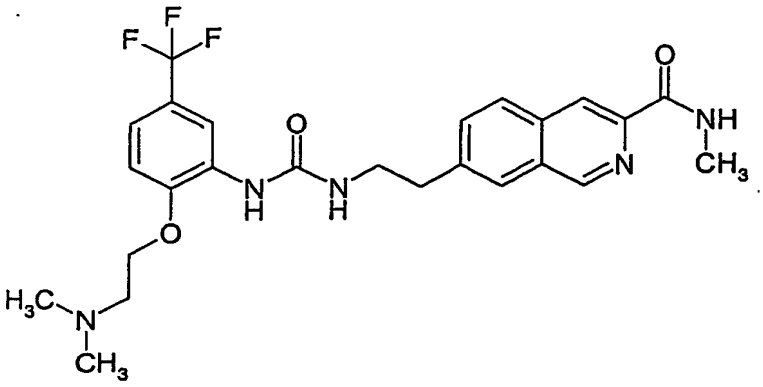
7-{2-[3-(4-Chloro-2-methoxy-5-methyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide (MW = 426.918; Rt = 2.49)



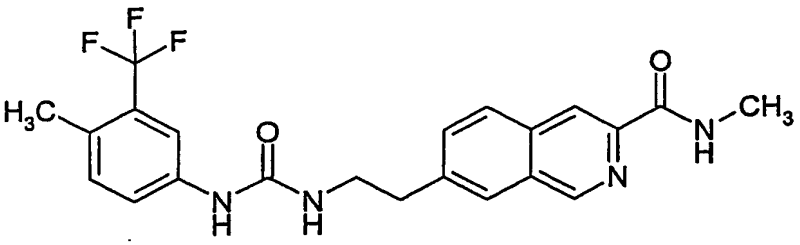
7-{2-[3-(Fluoro-trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide (MW = 434.40; Rt = 2.51);

and the pharmaceutically acceptable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios, and more preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

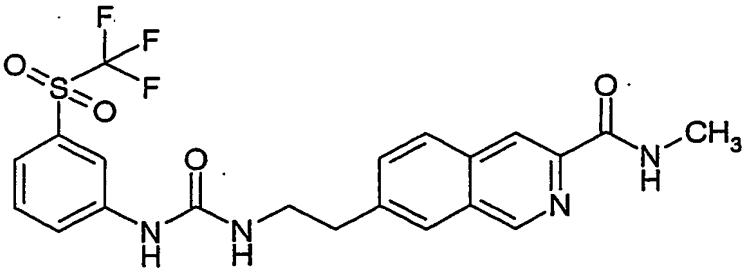
Especially preferred as compounds according to the invention are the compounds given below:



7-(2-{3-[(2-Dimethylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-ethyl)-isoquinoline-3-carboxylic acid methylamide;

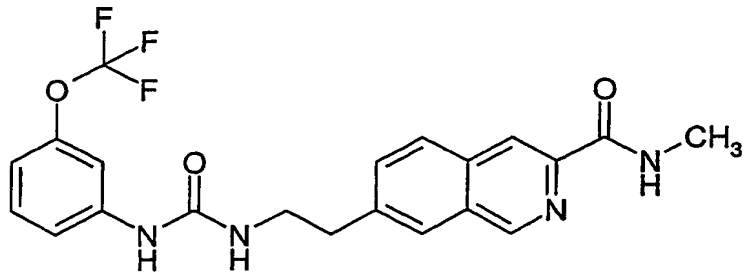


7-{2-[3-(4-Methyl-3-trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;

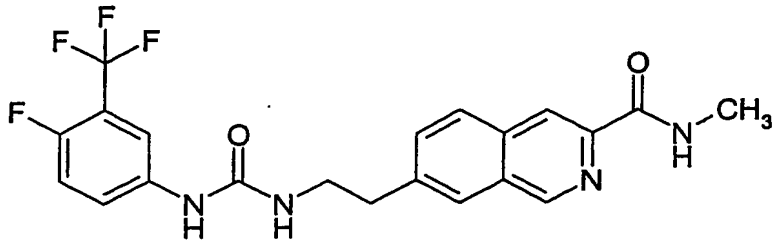


7-{2-[3-(3-Trifluoromethanesulfonyl-phenyl)-ureido]-ethyl}-isoquinoline-3-

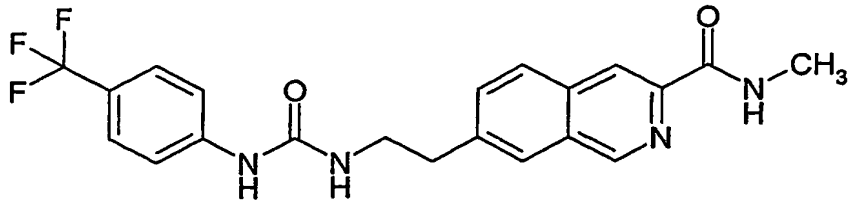
carboxylic acid methylamide;



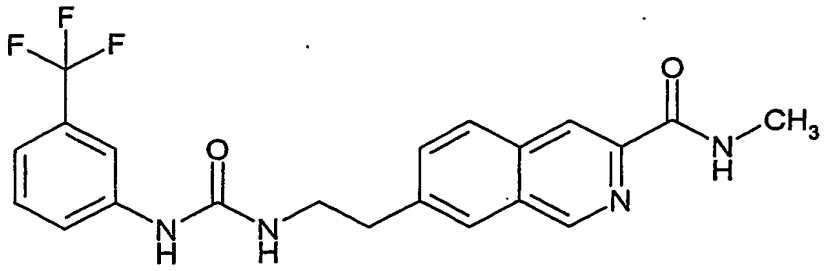
7-{2-[3-(3-Trifluoromethoxy-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide



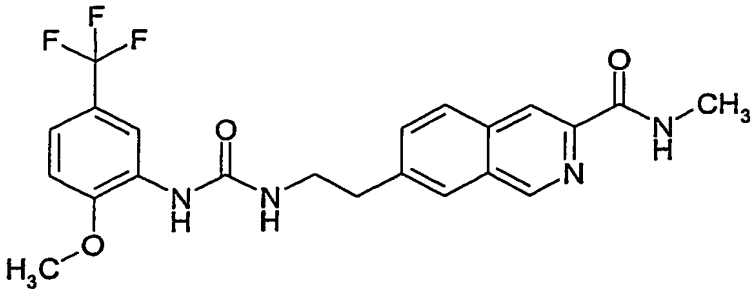
7-{2-[3-(4-Fluoro-3-trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;



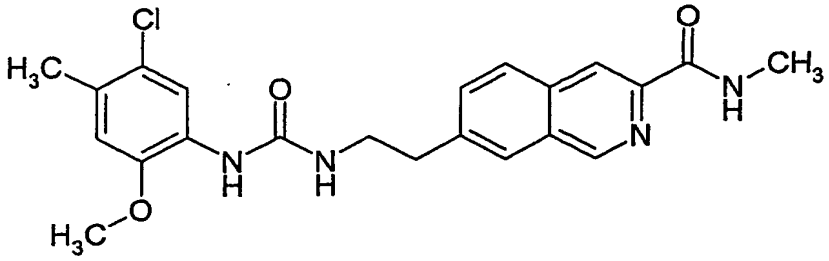
7-{2-[3-(4-Trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;



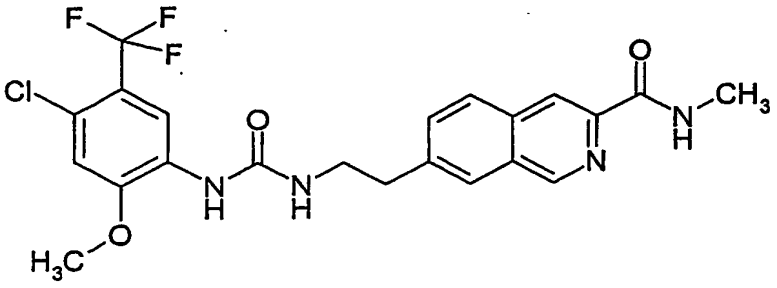
7-{2-[3-(3-Trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;



7-{2-[3-(2-Methoxy-5-trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;



7-{2-[3-(5-Chloro-2-methoxy-4-methyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;



7-{2-[3-(4-Chloro-2-methoxy-5-trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;

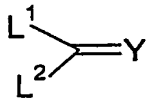
and the pharmaceutically acceptable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios, and more

preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

The nomenclature as used herein for defining compounds, especially the compounds according to the invention, is in general based on the rules of the IUPAC-organisation for chemical compounds and especially organic compounds.

Another aspect of the invention relates to a method for producing compounds of formula I, characterised in that

a) a compound of formula II,



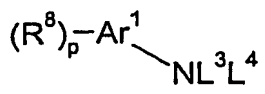
II

wherein

L^1 and L^2 either independently from one another represent a leaving group, or together represent a leaving group, and Y is as defined above/below,

is reacted with

b) a compound of formula III



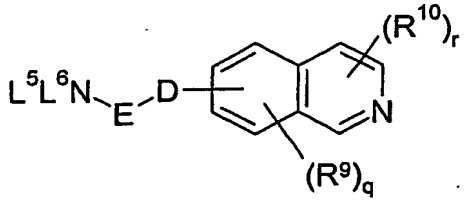
III

wherein

L^3 and L^4 are independently from one another H or a metal ion, and wherein R^8 and p are as defined above and below,

and

c) a compound of formula IV,



IV

wherein

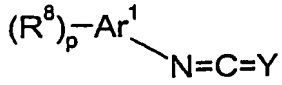
L^5 and L^6 are independently from one another H or a metal ion, and E, D, R^9, q, R^{10} and r are as defined above and below,

and optionally

d) isolating and/or treating the compound of formula I obtained by said reaction with an acid, to obtain the salt thereof.

Another aspect of the invention relates to an alternative method for producing compounds of formula I, characterised in that

a) a compound of formula IIIb



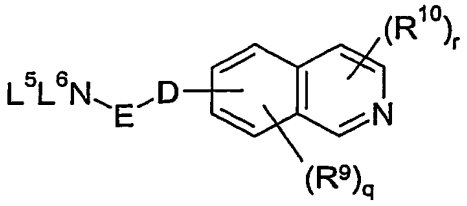
IIIb

wherein

wherein R^8, Ar^1, p and Y are as defined above and below,

and

b) a compound of formula IV,



IV

wherein

L^5 and L^6 are independently from one another H or a metal ion, and E, D, R^9, q, R^{10} and r are as defined above and below,

and optionally

c) isolating and/or treating the compound of formula I obtained by said reaction with an acid, to obtain the salt thereof.

The compounds of the formula I and also the starting materials for their preparation can be prepared by methods known per se, i. e. as described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. Use can also be made here of variants which are known per se, but are not mentioned here in greater detail.

If desired, the starting materials can also be formed in situ by not isolating them from the reaction mixture, but instead immediately converting them

further into the compounds of the formula I. On the other hand, it is possible to carry out the reaction stepwise.

The compounds according to the invention can be manufactured or produced in an advantageous manner according to the methods of manufacture as described herein.

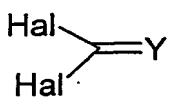
The reaction for the manufacture of compounds of formula I as described herein can be characterised as a carbonylation reaction of amines or the reaction of amines with carbon dioxide, carbon disulphide or derivatives or analogues thereof.

According to one aspect of the method according to the invention, in the compounds of formula II, L^1 and L^2 are preferably selected independently from one another from suitable leaving groups. Suitable leaving groups L^1 and L^2 for this type of reaction are known in the art, for example from the literature cited above. More preferably, L^1 and L^2 are independently selected from halogen, OR^{25} and $O\text{-}SO_2\text{-}R^{25}$. The residue R^{25} is preferably selected from substituted or unsubstituted alkyl groups and substituted or unsubstituted aryl groups, preferably substituted alkyl groups and substituted aryl groups. Preferred as alkyl groups in this respect are C_1-C_4- alkyl groups. Preferred as aryl group in this respect is phenyl. Suitable substituents for substituted alkyl groups are preferably selected from electronegative and/or electron withdrawing groups. Examples of electronegative and/or electron withdrawing groups for substituted alkyl groups include, but are not limited to halogen, especially Cl and/or F, cyano groups and nitro groups. Suitable substituents for substituted aryl groups are preferably selected from alkyl groups, preferably C_1 –C_4 alkyl groups, and electronegative and/or electron withdrawing groups. Examples of electronegative and/or electron withdrawing groups for substituted aryl groups include, but are not limited to halogen, especially Cl and/or F, cyano groups and nitro groups. If R^{25} is an unsubstituted alkyl group, it is preferably methyl. If R^{25} his a substituted alkyl

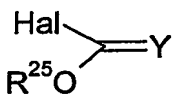
group, it is preferably CF_3 or CCl_3. If R^{25} is an unsubstituted aryl group, it is preferably phenyl. If R^{25} is a substituted aryl group, it is preferably selected from para- tolyl- (i. e. p-Me-C_6H_4) and para-Nitro-phenyl (i.e the p-O_2N-C_6H_4).

Even more preferably, the leaving groups OR^{25} are selected from the para-Tosyl- (i. e. p-Me-C_6H_4-SO_3-) group, the para-Nitro-phenolate- (i.e the p-O_2N-C_6H_4-O-) group and the triflate- (i. e. the F_3C-SO_3-) group.

Preferably, compounds of formula II, wherein L^1 and L^2 are selected independently from one another from suitable leaving groups, are selected from compounds IIa, IIb and IIc,

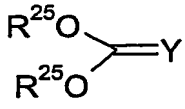


IIa



IIb

and

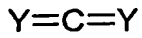


IIc

wherein Y, Hal and OR^{25} are as described above/below.

According to another aspect of the method according to the invention, in the compounds of formula II, L^1 and L^2 together represent a leaving group. In this aspect, L^1 and L^2 together preferably represent Y as the leaving group, wherein the leaving group Y is as defined above/below and more preferably is O or S.

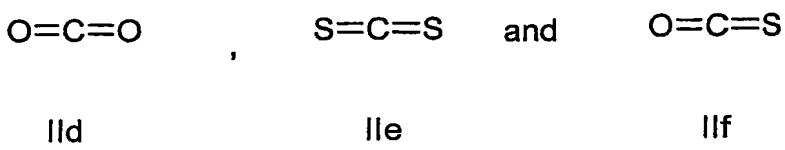
According to this aspect of the method according to the invention, the compound of formula II is a compound of formula II',



II'

wherein each Y is independently selected from the meaning given above/below, and especially is independently selected from O and S.

According to this aspect of the method according to the invention, the compound of formula II is preferably selected from compounds of formula IId, formula IIe and formula IIf,



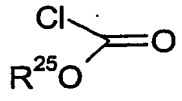
IId IIe IIf

more preferably of compounds of formula IId and formula IIe. In this aspect, compounds of formula IIa are especially preferred.

In compounds of formula II, Y is preferably selected from O and S, and more preferably is O.

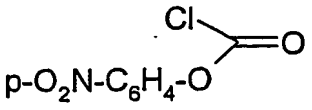
If compounds of formula II are desired wherein Y is other than O, it can be advantageous however to carry out the reaction according to the invention selecting a compound of formula II wherein Y is O, and to modify or convert the corresponding C=O group (i. e. the C=Y group, wherein Y is O) in the compound of formula I into a $C=NR^{21}$, $C=C(R^{22})-NO_2$, $C=C(R^{22})-CN$ or $C=C(CN)_2$ group according to methods known in the art, for example from Houben-Weyl, Methods of Organic Chemistry.

In the method of manufacture according to the invention, the compound of formula II is even more preferably a compound of formula IIg,



IIg

wherein R^{25} is as defined above/below, and especially a compound of formula IIh,



IIh.

In the compounds of formula III, L^3 and/or L^4 is preferably H or a moiety which activates the amino group it is bonded to, for example a metal ion. Suitable metal ions are preferably selected from the group consisting of alkaline metal ions, alkaline-earth metal ions and aluminium ions. Especially preferred metal ions are alkaline metal ions, of which Li, Na and K are especially preferred.

In the compounds of formula IV, L^5 and/or L^6 is preferably H or a moiety which activates the amino group it is bonded to, for example a metal ion. Suitable metal ions are preferably selected from the group consisting of alkaline metal ions, alkaline-earth metal ions and aluminium ions. Especially preferred metal ions are alkaline metal ions, of which Li, Na and K are especially preferred.

In case of multi-valent metal ions, the metal ions and the compounds of formula III and IV, respectively, form a complex containing one or more compounds of formula III and one or more metal ions wherein the ratio between the respective compounds and metal ions is depending on the valency of the metal ion(s) according to the rules of stoichiometry and/or electroneutrality.

In detail, the reaction of the compounds of formula II, formula III and formula IV is carried out in the presence or absence of a preferaby inert solvent at temperatures between about –20 °C and about 200 °C, preferably between –10 °C and 150 °C and especially between 0 °C or room temperature (25°) and 120°. In many cases, it is advantageous to combine one compound of formula III with one compound of formula IV at the lower end of the given temperature range, preferably between –20 °C and 75 °C, more preferred

between 0 °C and 60 °C and especially between 10 °C and 40 °C, for example at about room temperature, and heat the mixture up to a temperature at the upper end of the given temperature range, preferably between 65 °C and 180 °C, more preferred between 75 °C and 150 °C and especially between 80 °C and 120 °C, for example at about 80 °C, at about 90 °C or at about 100 °C. Proceeding in that manner can be advantageous in the case that pound of formula II is the compounds of formula II'. If the compound of formula II is not a compound of formula II', the reaction can be regularly carried out without prolonged heating to higher temperatures. For example, it can preferably be carried out at a temperature between –10 °C and 60 °C, more preferably between –5 °C and 40 °C and even more preferably at about 0 °C or at about room temperature. This given temperature range is especially advantageous, if the compound of formula II is selected from compounds of formula IIa, IIb, IIc and especially is a compound of formula IIg or IIh.

The method for manufacture according to the invention is preferably carried out in the presence of an acid binding means, for example one or more bases. This is especially advantageous, if the compound of formula II is selected from compounds of formula IIa – IIc an even preferred if the compound is selected from the compounds of formula IIg or formula IIh.

Suitable acid binding means are known in the art. Preferred as acid binding means are inorganic bases and especially organic bases. Examples for inorganic bases are alkaline or alkaline-earth hydroxides, alkaline or alkaline-earth carbonates and alkaline or alkaline-earth bicarbonates or other salts of a weak acid and alkaline or alkaline-earth metals, preferably of potassium, sodium, calcium or cesium. Examples for organic bases are triethyl amine, diisopropyl ethyl amine (DIPEA), diaza bicyclo undecen (DBU), dimethyl aniline, pyridine or quinoline. If an organic base is used, it is advantageous in general to use a base with a boiling point that is higher than the highest reaction temperature employed during the reaction. Especially preferred as

organic bases are pyridine and DIPEA. In many cases it is advantageous to employ two different organic bases and especially to use pyridine and DIPEA.

Reaction times are generally in the range between some minutes and several days, depending on the reactivity of the respective compounds and the respective reaction conditions. Suitable reaction times are readily determinable by methods known in the art, for example reaction monitoring. Based on the reaction temperatures given above, suitable reaction times generally lie in the range 10 min and 36 hrs, preferably 30 min and 24 hrs and especially between 45 min and 18 hrs, for example about 1 h, about 2 hrs, about 4 hrs, about 6 or about 18 hrs.

Preferably, the reaction of the compounds of the formula II, III and IV is carried out in the presence of a suitable solvent, that is preferably inert under the respective reaction conditions. Examples of suitable solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichlorethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide, dimethylformamide (DMF) or N-methyl pyrrolidinone (NMP); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said solvents. Polar solvents are in general preferred. Examples for suitable polar solvents are chlorinated hydrocarbons, alcohols, glycol ethers, nitriles, amides and sulfoxides or mixtures thereof. More preferred are chlorinated hydrocarbons, especially dichloromethane, and amides, especially DMF. Especially preferred is dichloromethane.

In compounds of formula IIIb, –N=C=Y is preferably –N=C=O or –N=C=S and especially preferably –N=C=O.

If compounds of formula II are desired wherein Y is other than O, it can be advantageous however to carry out the reaction of a compound of formula IIIb, wherein Y is O, and a compound of formula IV according to the invention to obtain a compound of formula I, wherein Y is O, and to modify or convert the corresponding C=O group (i. e. the C=Y group, wherein Y is O) in the compound of formula I into a $C=NR^{21}$, $C=C(R^{22})-NO_2$, $C=C(R^{22})-CN$ or $C=C(CN)_2$ group according to methods known in the art, for example from Houben-Weyl, Methods of Organic Chemistry.

In detail, the reaction of the compounds of the formula IIIb with the compounds of the formula IV is carried out in the presence or absence of a preferaby inert solvent at temperatures between about –20 °C and about 200 °C, preferably between –10 °C and 150 °C and especially between 0 °C or room temperature (25°) and 120°. If –N=C=Y is is selected from –N=C=O or –N=C=S and especially is –N=C=O, the reaction can be regularly carried out without prolonged heating to higher temperatures. For example, it can preferably be carried out at a temperature between –10 °C and 60 °C, more preferably between –5 °C and 40 °C and even more preferably at about 0 °C or at about room temperature.

Reaction times are generally in the range between some minutes and several days, depending on the reactivity of the respective compounds and the respective reaction conditions. Suitable reaction times are readily determinable by methods known in the art, for example reaction monitoring. Based on the reaction temperatures given above, suitable reaction times generally lie in the range 10 min and 36 hrs, preferably 30 min and 24 hrs and especially between 45 min and 16 hrs, for example about 1 h, about 2 hrs, about 4 hrs, about 6 or about 16 hrs.

Preferably, the reaction of the compounds of the formula IIIb with the compounds of the formula IV is carried out in the presence of a suitable solvent, that is preferably inert under the respective reaction conditions. Examples of suitable solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichlorethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide, dimethylformamide (DMF) or N-methyl pyrrolidinone (NMP); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said solvents. Polar solvents are in general preferred. Examples for suitable polar solvents are chlorinated hydrocarbons, alcohols, glycol ethers, nitriles, amides and sulfoxides or mixtures thereof. More preferred are chlorinated hydrocarbons, especially dichloromethane, and sulfoxides, especially DMSO. Especially preferred is dichloromethane.

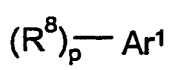
Preferably, the reaction between a compound of formula IIIb wherein –N=C=Y is –N=C=O or –N=C=S and especially is –N=C=O, and a compound of formula IV, especially a compound of formula IV, wherein L^1, L^2 and L^3 is H, is carried out in an inert solvent at the lower end of the given temperature range, for example in a chlorinated hydrocarbon, for example dichloromethane, in a temperature range between -10 °C and 60 °C, preferably at about 0 °C or at about room temperature. Reaction times generally lie in the range of 30 min hours to 24 hrs, preferably 1h to 6 hrs, for example at about 1h, at about 2 hrs, at about 3 hrs or about 5 hrs. Preferably, no acid binding means is present.

In general, the compounds of formula III, IIIb and/or formula IV are new. In any case, they can be prepared according to methods known in the art.

The compounds of formula IIIb can be obtained according to methods known in the art. In an advantageous manner, they can be readily obtained by one or more of the reaction routes given below:

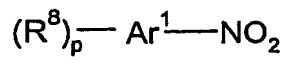
Compounds of formula IIIb, wherein Y is O or S can be readily obtained from suitable substituted derivatives of $(R^8)_p$-Ar^1 according to known procedures for producing isocyanates and thioisocyanates. When Y is O, the compounds of formula IIIb can be readily obtained via Curtius-, Hoffmann or Lossen rearrangement starting from $(R^8)_p$-Ar^1-COOH or the respective acid halides, as described in the art. If desired, compounds of formula III, wherein Y is O can be readily derivatized to compounds of formula IIIb, wherein Y is S or NR^{21}, according to procedures known in the art.

The compounds of formula III can be advantageously produced starting from a compound of formula (A)



(A)

wherein, R^8, p and Ar^1 are as defined above/below, and transferring it into a compound of formula (B);



(B)

according to methods known in the art. Advantageously, the compound of formula (A) then can be transferred into a compound of formula (B) by a nitration reaction. Suitable methods and reaction conditions for nitration reactions are known in the art. Advantageously, the compounds of formula

(A) can be obtained by reacting a compound of formula (B) with nitrating acid or a combination of concentrated sulfuric acid and potassium nitrate. If a combination of concentrated sulfuric acid and potassium nitrate is used, it can be advantageous to perform the reaction at a relatively low temperature, for example between -20 °C and + 50 °C, preferably between -10 °C and room temperature, more preferred between -5 °C and 0 °C.

The compound of formula (B) then can be transferred into the compound of formula III by methods known in the art.

The compound of formula (B) then can be transferred into a compound of formula III according to methods known in the art.

Advantageously, the compound of formula (B) can be transferred into a compound of formula III, wherein L^3 and L^4 are hydrogen, preferably by a reduction reaction or hydrogenating reaction, preferably a hydrogenating reaction. Methods and reaction conditions for hydrogenating a NO_2-moiety into a NH_2-moiety are known in the art. In general, it is advantageous to carry out the hydrogenation reaction in a hydrogen atmosphere in the presence of a suitable catalyst, for example Pd/C or Raney-nickel, preferably Raney-nickel. In general, such hydrogenation reactions are carried out in a suitable solvent. Suitable solvents for hydrogenation reactions are known in the art. Suitable solvents, for example, are alcohols, especially methanol and ethanol and ethers, especially THF, and mixtures thereof. Preferred as solvent is a mixture of THF/methanol, preferably in about equal measures. In general, the hydrogenation reactions are carried out at about normal pressure or slightly elevated pressure, for example between normal pressure and 3 bar pressure (about 300 kPa). The hydrogenation reaction is usually carried out in the temperature range between -20° and 150°, preferably 0° and 50°. The obtained compound of formula III wherein L^3 and L^4 are hydrogen can optionally be isolated and/or purified and then optionally transferred into a

compound of formula III wherein L^3 and L^4 are other than hydrogen, for example according to methods and reaction conditions as described herein.

The compounds of formula IV can be obtained according to methods known in the art, for example as described in Houben-Weyl, Methods of Organic Chemistry. For example, they can be prepared according to known procedures for preparing isoquinolines, such as the Bischler-Napieralski reaction and/or the so-called modified Gabriel-synthesis, or in an analogues manner therof.

The compounds of formula IV can be obtained according to methods known in the art. In an advantageous manner, they can be readily obtained by one or more of the reaction routes given below:

If the compound is a compound of formula IVa, it can be readily obtained from a compound of formula Va, for example by a reduction reaction or hydrogenating reaction. Suitable reduction or hydrogenating reactions are known in the art. In an advantageous manner, the compound of formula IVa can be obtained by hydrogenating a compound of formula V

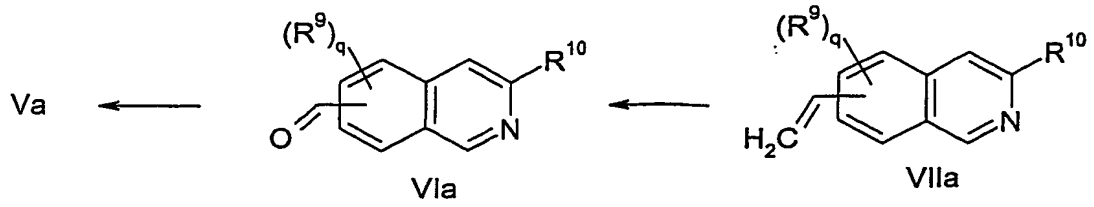
The compounds of formula IV can be obtained according to methods known in the art, for example as described in Houben-Weyl, Methods of Organic Chemistry. For example, they can be prepared according to known procedures for preparing isoquinolines, such as the Bischler-Napieralski reaction and/or the so-called modified Gabriel-synthesis, or in an analogues manner therof.

The compounds of formula IV can be obtained according to methods known in the art. In an advantageous manner, they can be readily obtained by one or more of the reaction routes given below:

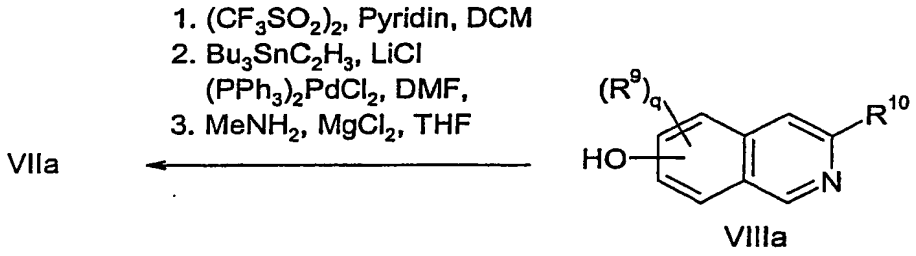
If the compound is a compound of formula IVa, it can be readily obtained from a compound of formula Va, for example by a reduction reaction or

hydrogenating reaction. Suitable reduction or hydrogenating reactions are known in the art. In an advantageous manner, the compound of formula IVa can be obtained by hydrogenating a compound of formula Va in the presence of a hydrogen delivering means, for example hydrogen gas, in the presence of a suitable catalyst, preferably a Nickel catalyst, for example Raney-Nickel. In general, such hydrogenation reactions are carried out in a suitable solvent. Suitable solvents for hydrogenation reactions are known in the art. Suitable solvents, for example, are alcohols, especially methanol and ethanol and ethers, especially THF, and mixtures thereof. Preferably, the hydrogenation reaction is carried out in a methanol/ammonia mixture, preferably in the presence of Raney nickel. In general, the hydrogenation reactions are carried out at about normal pressure or elevated pressure, for example between normal pressure and 10 bar pressure, preferably at about 5 par pressure (about 500 kPa). The hydrogenation reaction is usually carried out in the temperature range between -20 °C and 150 °C, preferably +20 °C and 100 °C, for example at about 45 °C.

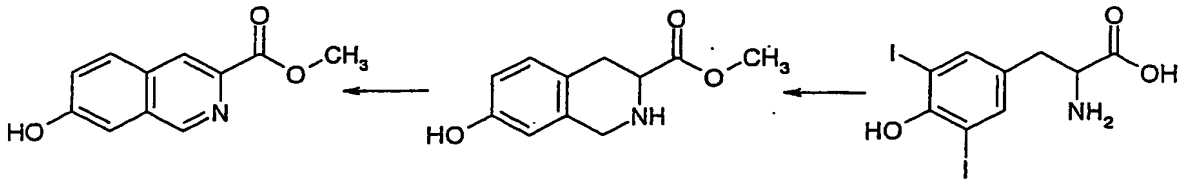
The compound of formula Va can be obtained in an advantageous manner starting from a compound of formula VIIa and oxidising it into a compound of formula VIa for example in the presence of a suitable catalyst, such as OsO_4. The thus obtained compound of formula VIa can be transformed into a compound of formula Va according to methods known in the art. In an advantageous manner, it can be transferred by erecting a compound of formula VIa subsequently with a reduction agent, such as hydrides, preferably $NaBH_4$, in a suitable solvent, such as methanol, then halogenating, preferably chlorinating the compound obtained from the reducing step and reacting the compound obtained from the halogenating step with a cyanide, for example sodium cyanide or potassium cyanide.



The compound of formula VIIa can be readily obtained from a compound of formula VIIIa according to methods known in the art. In an advantageous manner, it can be obtained starting from a compound of formula VIIIa according to the reaction scheme given below:

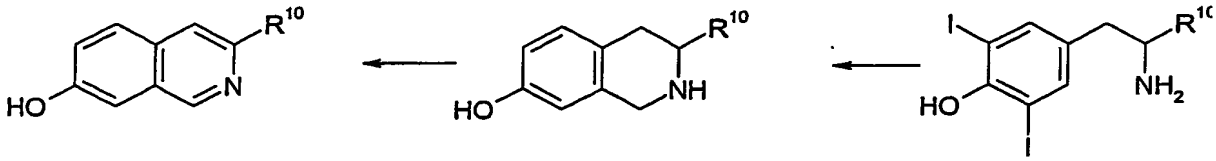


Compounds of formula VIIIa can be produced according to methods known in the art. If the compound of formula VIIIa is a compound of formula VIIIaa, it can be advantageously obtained by starting with a compound of formula Xaa by a cyclization reaction with a C_1-compound, such as formaldehyde, reducing the product obtained from the cyclization step, for example with hydrogen in the presence of a suitable catalyst, such as Pd/C, and subjecting the thus obtained compound of formula IXaa to a dehydrogenation reaction, such as a transfer dehydrogenation reaction in the presence of a suitable catalyst, such as Pd/C, and a suitable aromatic solvent, such as xylene.



VIIIaaa IXaaa Xaaa

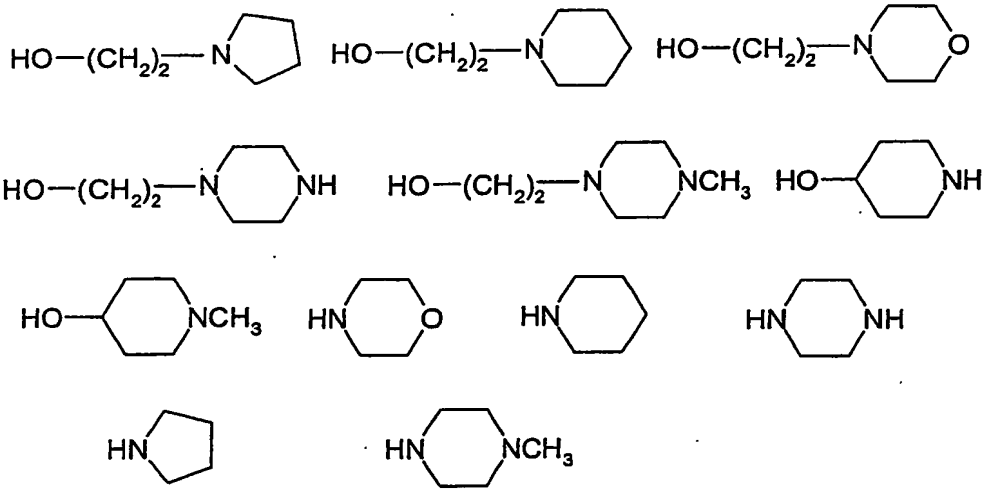
This reaction sequence is especially advantageous if starting with a compound of formula Xaa, wherein R^{10} is COOH. If starting with this compound, it is advantageous to protect the COOH moiety, for example by transferring it into the respective ether, then subsequently performing the cyclisation reaction, reduction reaction and the dehydrogenation reaction, for example as described above, to obtain the desired compound of formula VIIIaaa, wherein R^{10} is $COOCH_3$. Optionally, the residue R^{10} can then be transferred into other moieties R^{10}, for example into a moiety R^{10} which is CONHA or $COONHCH_3$, by methods known in the art, such as a saponification step and/or an amidation step.



VIIIaa IXaa Xaa

Independently of the chosen reaction route, it is in many cases possible or even feasible to introduce residues R^8, R^9 and/or R^{10} into one or more of the compounds described above, or, if the compound already comprises one or more residues R^8, R^9 and/or R^{10}, to introduce additional residues R^8, R^9 and/or R^{10} into said compound. The introduction of additional residues can be readily performed by methods known in the art and especially by aromatic substitution, for example nucleophilic aromatic substitution or electrophilic aromatic substitution. For example, in compounds comprising Ar^1, wherein Ar^1 comprises one or more halogen and preferably fluorine substituents, one or more of the halogen/fluorine substituents can be easily substituted by hydroxy, thio and/or amino substituted hydrocarbons, preferably selected

from the group consisting of $HO(CH_2)_kNR^{11}R^{12}$, $HO(CH_2)_kR^{13}$, $HO(CH_2)_kOR^{11}$, $HO(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $HO(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $HO(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $HO(CH_2)_nCOOR^{13}$, $HO(CH_2)_nS(O)_uR^{13}$, $HNR^{11}(CH_2)_kNR^{11}R^{12}$, $HNR^{11}(CH_2)_kOR^{11}$, $HNR^{11}(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $HNR^{11}(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $HNR^{11}(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $HNR^{11}(CH_2)_nCOOR^{12}$ and $HNR^{11}(CH_2)_nS(O)_uR^{13}$, and the metal salts thereof, wherein R^{11}, R^{12} and R^{13} are defined as above and n is as defined above, preferably n is 0, 1 or 2 and especially is 0, k is 1 to 4 and preferably 1 or 2, and u is preferably 2. Even more preferred, the hydroxy, thio and/or amino substituted hydrocarbons are selected from the group consisting of NH_3, $HN(CH_3)_2$, NH_2CH_3, $HN(C_2H_5)_2$, $H_2NCH_2CH_2NH_2$, $HOCH_2CH_2NH_2$, $HOCH_2CH_2NHCH_3$, $HN(CH_3)CH_2CH_2NH_2$, $HN(CH_3)CH_2CH_2N(CH_3)_2$, $HN(CH_3)CH_2CH_2N(CH_3)_2$, $HN(CH_3)CH_2CH_2OCH_3$, $HOCH_2CH_2N(CH_3)_2$, $HOCH_2CH_2N(CH_2CH_3)_2$, $HSCH_3$, HSC_2H_5, and compounds of the formulae



or salts and especially metal salts thereof.

On the other hand, it is in many cases possible or even feasible to modify or derivatize one or more of the residues R^8, R^9 and/or R^{10} into residues R^8, R^9 and/or R^{10} other than the ones originally present. For example, CH_3-groups can be oxidized into aldehyde groups or carboxylic acid groups, thio atom

containing groups, for example S-alkyl or S-aryl groups, can be oxidized into SO_2-alkyl or SO_2-aryl groups, respectively, carboxylic acid groups can be derivatized to carboxylic acid ester groups or carboxylic acid amide groups and carboxylic acid ester groups or carboxylic acid amide groups can be hydrolysed into the corresponding carboxylic acid groups. Methods for performing such modifications or derivatizations are known in the art, for example from Houben-Weyl, Methods of Organic Chemistry.

Every reaction step described herein can optionally be followed by one or more working up procedures and/or isolating procedures. Suitable such procedures are known in the art, for example from standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart). Examples for such procedures include, but are not limited to evaporating a solvent, distilling, crystallization, fractionised crystallization, extraction procedures, washing procedures, digesting procedures, filtration procedures, chromatography, chromatography by HPLC and drying procedures, especially drying procedures in vacuo and/or elevated temperature.

A base of the formula I can be converted into the associated acid-addition salt using an acid, for example by reaction of equivalent amounts of the base and the acid in a preferably inert solvent, such as ethanol, followed by evaporation. Suitable acids for this reaction are, in particular, those which give physiologically acceptable salts. Thus, it is possible to use inorganic acids, for example sulfuric acid, sulfurous acid, dithionic acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as, for example, orthophosphoric acid, sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid, propionic acid, hexanoic acid, octanoic acid, decanoic acid, hexadecanoic acid, octadecanoic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid pimelic acid, fumaric acid,

maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, trimethoxybenzoic acid, adamantanecarboxylic acid, p-toluenesulfonic acid, glycolic acid, embonic acid, chlorophenoxyacetic acid, aspartic acid, glutamic acid, proline, glyoxylic acid, palmitic acid, parachlorophenoxyisobutyric acid, cyclohexanecarboxylic acid, glucose 1-phosphate, naphthalenemono- and -disulfonic acids or laurylsulfuric acid. Salts with physiologically unacceptable acids, for example picrates, can be used to isolate and/or purify the compounds of the formula I. On the other hand, compounds of the formula I can be converted into the corresponding metal salts, in particular alkali metal salts or alkaline earth metal salts, or into the corresponding ammonium salts, using bases (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate). Suitable salts are furthermore substituted ammonium salts, for example the dimethyl-, diethyl- and diisopropylammonium salts, monoethanol-, diethanol- and diisopropanolammonium salts, cyclohexyl- and dicyclohexylammonium salts, dibenzylethylenediammonium salts, furthermore, for example, salts with arginine or lysine.

On the other hand, if desired, the free bases of the formula I can be liberated from their salts using bases (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate).

The invention relates to compounds of the formula I and physiologically acceptable salts and solvates thereof as medicaments.

The invention also relates to the compounds for the formula I and physiologically acceptable salts and solvates thereof as kinase inhibitors.

The invention furthermore relates to the use of the compounds of the formula I and/or physiologically acceptable salts and/or solvates thereof for the

preparation of pharmaceutical compositions and/or pharmaceutical preparations, in particular by non- chemical methods. In this cases, one or more compounds according to the invention can be converted into a suitable dosage form together with at least one solid, liquid and/or semi-liquid excipient or adjuvant and, if desired, in combination with one or more further active ingredients.

The invention further relates to the use of one or more of the compounds according to the invention, selected from the group consisting of compounds of the formula I as free bases, solvates of compounds of the formula I, salts of compounds of formula I, for the production of pharmaceutical compositions and/or pharmaceutical preparations, in particular by a non-chemical route. In general, non-chemical routes for the production of pharmaceutical compositions and/or pharmaceutical preparations comprise processing steps on suitable mechanical means known in the art that transfer one or more compounds according to the invention into a dosage form suitable for administration to a patient in need of such a treatment. Usually, the transfer of one or more compounds according to the invention into such a dosage form comprises the addition of one or more compounds, selected from the group consisting of carriers, excipients, auxiliaries and pharmaceutical active ingredients other than the compounds according to the invention. Suitable processing steps include, but are not limited to combining, milling, mixing, granulating, dissolving, dispersing, homogenizing, casting and/or compressing the respective active and non-active ingridients. In this respect, active ingredients are preferably at least one compound according to this invention and one or more additional compounds other than the compounds according to the invention, which show valuable pharmaceutical properties, preferably those pharmaceutical active agents other than the compounds according to invention which are disclosed herein.

The process for preparing pharmaceutical compositions and/or pharmaceutical preparations preferably comprises one or more processing

steps, selected from the group consisting of combining, milling, mixing, granulating, dissolving, dispersing, homogenizing and compressing. The one or more processing steps are preferably performed on one or more of the ingredients which are to form the pharmaceutical composition and/or pharmaceutical preparation preferably according to invention. Even more preferred, said processing steps are performed on two or more of the ingredients which are to form the pharmaceutical composition and/or pharmaceutical preparation, said ingredients comprising one or more compounds according to the invention and, additionally, one or more compounds, preferably selected from the group consisting of active ingredients other than the compounds according to the invention, excipients, auxiliaries, adjuvants and carriers. Mechanical means for performing said processing steps are known in the art, for example from Ullmann's Encyclopedia of Industrial Chemistry, 5th Edition.

Preferably, one or more compounds according to the invention are converted into a suitable dosage form together with at least one compound selected from the group consisting of excipients, auxiliaries, adjuvants and carriers, especially solid, liquid and/or semi-liquid excipients, auxiliaries, adjuvants and carriers, and, if desired, in combination with one or more further active ingredients.

Suitable dosage forms include, but are not limited to tablets, capsules, semi-solids, suppositories, aerosols, which can be produced according to methods known in the art, for example as described below:

tablets	mixing of active ingredient/s and auxiliaries, compression of said mixture into tablets (direct compression), optionally granulation of part of mixture before compression

capsules	mixing of active ingredient/s and auxiliaries to obtain a flowable powder, optionally granulating powder, filling powders/granulate into opened capsules, capping of capsules
semi-solids (ointments, gels, creams)	dissolving/dispersing active ingredient/s in an aqueous or fatty carrier; subsequent mixing of aqueous/fatty phase with complementary fatty resp. aqueous phase, homogenisation (creams only)
suppositories (rectal and vaginal)	dissolving/dispersing active ingredient/s in carrier material liquified by heat (rectal: carrier material normally a wax; vaginal: carrier normally a heated solution of a gelling agent), casting said mixture into suppository forms, annealing and withdrawal suppositories from the forms
aerosols:	dispersing/dissolving active agent/s in a propellant, bottling said mixture into an atomizer

The invention thus relates to pharmaceutical compositions and/or pharmaceutical preparations comprising at least one compound of the formula I and/or one of its physiologically acceptable salts and/or solvates.

Preferably, the pharmaceutical compositions and/or pharmaceutical preparations according to the invention contain a therapeutic effective amount of one or more compounds according to the invention. Said therapeutic effective amount of one or more of the compounds according to the invention is known to the skilled artisan or can be easily determined by

standard methods known in the art. For example, the compounds according to the invention can be administered to a patient in an analogous manner to other compounds that are effective as raf-kinase inhibitors, especially in an analogous manner to the compounds described in WO 00/42012 (Bayer). Usually, suitable doses that are therapeutically effective lie in the range between 0.0005 mg and 1000 mg, preferably between 0.005 mg and 500 mg and especially between 0.5 and 100 mg per dose unit. The daily dose comprises preferably more than 0.001 mg, more preferred more than 0.01 milligram, even more preferred more than 0.1 mg and especially more than 1.0 mg, for example more than 2.0 mg, more than 5 mg, more than 10 mg, more than 20 mg, more than 50 mg or more than 100 mg, and preferably less than 1500 mg, more preferred less than 750 mg, even more preferred less than 500 mg, for example less than 400 mg, less than 250 mg, less than 150 mg, less than 100 mg, less than 50 mg or less than 10 mg.

The specific dose for the individual patient depends, however, on the multitude of factors, for example on the efficacy of the specific compounds employed, on the age, body weight, general state of health, the sex, the kind of diet, on the time and route of administration, on the excretion rate, the kind of administration and the dosage form to be administered, the pharmaceutical combination and severity of the particular disorder to which the therapy relates. The specific therapeutic effective dose for the individual patient can readily be determined by routine experimentation, for example by the doctor or physician which advises or attends the therapeutic treatment.

However, the specific dose for each patient depends on a wide variety of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and method of administration, on the rate of excretion, medicament combination and severity of the particular illness to which the therapy applies. Parenteral administration is preferred. Oral administration is especially preferred.

These compositions and/or preparations can be used as medicaments in human or veterinary medicine. Suitable excipients are organic or inorganic substances which are suitable for enteral (for example oral), parenteral or topical administration and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatine, carbohydrates, such as lactose or starch, magnesium stearate, talc or vaseline. Examples for suitable dosage forms, which are especially suitable for oral administration are, in particular, tablets, pills, coated tablets, capsulees, powders, granules, syrups, juices or drops. Further examples for suitable dosage forms, which are especially suitable for rectal administration are suppositories, further examples for suitable dosage forms, which are especially suitable for parenteral administration are solutions, preferably oil-based or aqueous solutions, furthermore suspensions, emulsions or implants, and suitable for topical application are ointments, creams or powders. The novel compounds may also be lyophilised and the resultant lyophilisates used, for example, for the preparation of injection preparations. The compositions and/or preparations indicated may be sterilized and/or comprise assistants, such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for modifying the osmotic pressure, buffer substances, dyes and flavors and/or one or more further active ingredients, for example one or more vitamins.

For administration as an inhalation spray, it is possible to use sprays in which the active ingredient is either dissolved or suspended in a propellant gas or propellant gas mixture (for example CO_2 or chlorofluorocarbons). The active ingredient is advantageously used here in micronized form, in which case one or more additional physiologically acceptable solvents may be present, for example ethanol. Inhalation solutions can be administered with the aid of conventional inhalers.

The compounds of the formula I and their physiologically acceptable salts and solvates can be employed for combating one or more diseases, for example allergic diseases, psoriasis and other skin diseases, especially melanoma, autoimmune diseases, such as, for example, rheumatoid arthritis, multiple sclerosis, Crohn's disease, diabetes mellitus or ulcerative colitis.

In General, the substances according to the invention are preferably administered in doses corresponding to the compound rolipram of between 1 and 500 mg, in particular between 5 and 100 mg per dosage unit. The daily dose is preferably between about 0.02 and 10 mg/kg of body weight. However, the specific dose for each patient depends on a wide variety of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and method of administration, on the excretion rate, medicament combination and severity of the particular illness to which the therapy applies. Oral administration is preferred.

The compounds of the formula I according to claim 1 and/or their physiologically acceptable salts are also used in pathological processes which are maintained or propagated by angiogenesis, in particular in tumors, restenoses, diabetic retinopathy, macular degenerative disease or rheumatois arthritis.

Those of skill will readily appreciate that dose levels can vary as a function of the specific compound, the severity of the symptoms and the susceptibility of the subject to side effects. Some of the specific compounds are more potent than others. Preferred dosages for a given compound are readily determinable by those of skill in the art by a variety of means. A preferred means is to measure the physiological potency of a given compound.

For use in the subject methods, the subject compounds may be formulated with pharmaceutically active agents other than the compounds according to

the invention, particularly other anti-metastatic, antitumor or anti-angiogenic agents. Angiostatic compounds of interest include angiostatin, enclostatin, carboxy terminal peptides of collagen alpha (XV), etc. Cytotoxic and cytostatic agents of interest include adriamycin, aleran, Ara-C, BICNU, busulfan, CNNU, cisplatinum, cytoxan, daunorubicin, DTIC, 5-FU, hydrea, ifosfamicle, methotrexate, mithramycin, mitomycin, mitoxantrone, nitrogen mustard, velban, vincristine, vinblastine, VP-16, carboplatinum, fludarabine, gemcitabine, idarubicin, irinotecan, leustatin, navelbine, taxol, taxotere, topotecan, etc.

The compounds of the invention have been shown to have antiproliferative effect in an in vivo xenograft tumor model. The subject compounds are administered to a subject having a hyperproliferative disorders, e.g., to inhibit tumor growth, to decrease inflammation associated with a lymphoproliferative disorder, to inhibit graft rejection, or neurological damage due to tissue repair, etc. The present compounds are useful for prophylactic or therapeutic purposes. As used herein, the term "treating" is preferably also used to refer to both prevention of disease, and treatment of pre-existing conditions. The prevention of proliferation is accomplished by administration of the subject compounds prior to development of overt disease, e.g., to prevent the regrowth of tumors, prevent metastatic growth, diminish restenosis associated with cardiovascular surgery, etc. Alternatively the compounds are used to treat ongoing disease, by stabilizing or improving the clinical symptoms of the patient.

The host, or patient, may be from any mammalian species, e.g., primate sp., particularly human; rodents, including mice, rats and hamsters; rabbits; equines, bovines, canines, felines; etc. Animal models are of interest for experimental investigations, providing a model for treatment of human disease.

The susceptibility of a particular cell to treatment with the subject compounds may be determined by in vitro testing. Typically a culture of the cell is combined with a subject compound at varying concentrations for a period of time sufficient to allow the active agents to induce cell death or inhibit migration, usually between about one hour and one week. For in vitro testing, cultured cells from a biopsy sample may be used. The viable cells left after treatment are then counted.

The dose will vary depending on the specific compound utilized, specific disorder, patient status, etc. Typically a therapeutic dose will be sufficient to substantially decrease the undesirable cell population in the targeted tissue, while maintaining patient viability. Treatment will generally be continued until there is a substantial reduction, e.g., at least about 50 %, decrease in the cell burden, and may be continued until there are essentially none of the undesirable cells detected in the body.

The compounds according to the invention are preferably administered to human or nonhuman animals, more preferred to mammalian animals and especially to humans.

The compounds also find use in the specific inhibition of a signaling pathway mediated by protein kinases. Protein kinases are involved in signaling pathways for such important cellular activities as responses to extracellular signals and cell cycle checkpoints. Inhibition of specific protein kinases provided a means of intervening in these signaling pathways, for example to block the effect of an extracellular signal, to release a cell from cell cycle checkpoint, etc. Defects in the activity of protein kinases are associated with a variety of pathological or clinical conditions, where there is a defect in the signaling mediated by protein kinases. Such conditions include those associated with defects in cell cycle regulation or in response to extracellular signals, e.g., immunological disorders, autoimmune and immunodeficiency diseases; hyperproliferative disorders, which may include psoriasis, arthritis,

inflammation, endometriosis, scarring, cancer, etc. The compounds of the present invention are active in inhibiting purified kinase proteins preferably raf kinases, e.g., there is a decrease in the phosphorylation of a specific substrate in the presence of the compound. The compounds of the invention may also be useful as reagents for studying signal transduction or any of the clinical disorders listed throughout this application.

There are many disorders associated with a dysregulation of cellular proliferation. The conditions of interest include, but are not limited to, the following conditions. The subject compounds are useful in the treatment of a variety of conditions where there is proliferation and/or migration of smooth muscle cells, and/or inflammatory cells into the intimal layer of a vessel, resulting in restricted blood flow through that vessel, e.g., neointimal occlusive lesions. Occlusive vascular conditions of interest include atherosclerosis, graft coronary vascular disease after transplantation, vein graft stenosis, peri-anastomatic prothetic graft stenosis, restenosis after angioplasty or stent placement, and the like.

Diseases where there is hyperproliferation and tissue remodelling or repair or reproductive tissue, e.g., uterine, testicular and ovarian carcinomas, endometriosis, squamous and glandular epithelial carcinomas of the cervix, etc. are reduced in cell number by administration of the subject compounds. The growth and proliferation of neural cells is also of interest.

Tumor cells are characterized by uncontrolled growth, invasion to surrounding tissues, and metastatic spread to distant sites. Growth and expansion requires an ability not only to proliferate, but also to down-modulate cell death (apoptosis) and activate angiogenesis to product a tumor neovasculature.

Tumors of interest for treatment include carcinomas, e.g., colon, duodenal, prostate, breast, melanoma, ductal, hepatic, pancreatic, renal, endometrial,

stomach, dysplastic oral mucosa, polyposis, invasive oral cancer, non-small cell lung carcinoma, transitional and squamous cell urinary carcinoma etc.; neurological malignancies; e.g. neuroplastoma, gliomas, etc.; hematological malignancies, e.g., childhood acute leukaemia, non-Hodgkin's lymphomas, chronic lymphocytic leukaemia, malignant cutaneous T-cells, mycosis fungoides, non-MF cutaneous T-cell-lymphoma, lymphomatoid papulosis, T-cell rich cutaneous lymphoid hyperplasia, bullous pemphigoid, discoid lupus erythematosus, lichen planus, etc.; and the like.

Tumors of neural tissue are of particular interest, e.g., gliomas, neuromas, etc. Some cancers of particular interest include breast cancers, which are primarily adenocarcinoma subtypes. Ductal carcinoma in situ is the most common type of noninvasive breast cancer. In DCIS, the malignant cells have not metastasized through the walls of the ducts into the fatty tissue of the breast. Infiltration (or invasive) ductal carcinoma (IDC) has metastasized through the wall of the duct and invaded the fatty tissue of the breast. Infiltrating (or invasive) lobular carcinoma (ILC) is similar to IDC, in that it has the potential to metastasize elsewhere in the body. About 10 % to 15 % of invasive breast cancers are invasive lobular carcinomas.

Also of interest is non-small cell lung carcinoma. Non-small cell lung cancer (NSCLC) is made up of three general subtypes of lung cancer. Epidermoid carcinoma (also called squamos cell carcinoma) usually starts in one of the larger bronchial tubes and grows relatively slowly. The size of these tumors can range from very small to quite large. Adenocarcinoma starts growing near the outside surface of the lung and may vary in both size and growth rate. Some slowly growing adenocarcinomas are described as alveolar cell cancer. Large cell carcinoma starts near the surface of the lung, grows rapidly, and the growth is usually fairly large when diagnosed. Other less common forms of lung cancer are carcinoid, cylindroma, mucoepidermoid, and malignant mesothelioma.

Melanoma is a malignant tumor of melanocytes. Although most melanomas arise in the skin, they also may arise from mucosal surfaces or at other sites to which neural crest cells migrate. Melanoma occurs predominantly in adults, and more than half of the cases arise in apparently normal areas of the skin. Prognosis is affected by clinical and histological factors and by anatomic location of the lesion. Thickness and/or level of invasion of the melanoma, mitotic index, tumor infiltrating lymphocytes, and ulceration or bleeding at the primary site affect the prognosis. Clinical staging is based on whether the tumor has spread to regional lymph nodes or distant sites. For disease clinically confined to the primary site, the greater the thickness and depth of local invasion of the melanoma, the higher the chance of lymph node metastases and the worse the prognosis. Melanoma can spread by local extension (through lymphatics) and/or by hematogenous routes to distant sites. Any organ may be involved by metastases, but lungs and liver are common sites.

Other hyperproliferative diseases of interest relate to epidermal hyperproliferation, tissue, remodeling and repair. For example, the chronic skin inflammation of psoriasis is associated with hyperplastic epidermal keratinocyctes as well as infiltrating mononuclear cells, including CD4+ memory T cells, neutrophils and macrophages.

The proliferation of immune cells is associated with a number of autoimmune and lymphoproliferative disorders. Diseases of interest include multiple sclerosis, rheumatoid arthritis and insulin dependent diabetes mellitus. Evidence suggests that abnormalities in apoptosis play a part in the pathogenesis of systemic lupus erythematosus (SLE). Other lymphoproliferative conditions the inherited disorder of lymphocyte apoptosis, which is an autoimmune lymphoproliferative syndrome, as well as a number of leukemia's and lymphomas. Symptoms of allergies to environmental and food agents, as well as inflammatory bowel disease, may also be alleviated by the compounds of the invention.

Surprisingly, it has been found that isoquinoline derivatives according to invention are able to interact with signaling pathways, especially the signaling pathways described herein and preferably the raf-kinase signaling pathway. Isoquinoline derivatives according to the invention preferably show advantageous biological activity which can easily be demonstrated according to methods known in the art, for example by enzyme based assays. Suitable assays are known in the art, for example from the literature cited herein and the references cited in the literature, or can be developed and/or performed in an analogous manner thereof. In such enzyme based assays, isoquinoline derivatives according to invention show an effect, preferably a modulating and especially an inhibiting effect which is usually documented by IC_{50} values in a suitable range, preferably in the micromolar range and more preferred in the nanomolar range.

In general, compounds according to the invention are to be regarded as suitable kinase-modulators and especially suitable kinase-inhibitors according to the invention if they show an effect or an activity to one or more kinases, preferably kinases as defined herein and especially preferably to one or more raf-kinases, that preferably lies, determined as IC_{50}-value, in the range of 100 µmol or below, preferably 10 µmol or below, more preferably in the range of 3 µmol or below, even more preferably in the range of 1 µmol or below and most preferably in the nanomolar range. Especially preferred for use according to the invention are kinase-inhibitors as defined above/below, that show an activity, determined as IC_{50}-value, to one or more kinases, preferably kinases as defined herein, more preferably one or more raf-kinases, especially preferably including A-raf, B-raf and c-raf1 or consisting of A-raf, B-raf and c-raf1 and even more preferred including c-raf1 or consisting of c-raf1, in the range of 0.5 µmol or below and especially in the range of 0.1 µmol or below. In many cases an IC_{50}-value at the lower end of the given ranges is advantageous and in some cases it is highly desirable that the IC_{50}-value is as small as possible or the he IC_{50}-values are as small as possible,

but in general IC_{50}-values that lie between the above given upper limits and a lower limit in the range of 0.0001 µmol, 0.001 µmol, 0.01 µmol or even above 0.1 µmol are sufficient to indicate the desired pharmaceutical activity. However, the activities measured can vary depending on the respective testing system or assay chosen.

Alternatively, the advantageous biological activity of the compounds according to the invention can easily be demonstrated in *in vitro* assays, such as *in vitro* proliferation assays or *in vitro* growth assays. Suitable *in vitro* assays are known in the art, for example from the literature cited herein and the references cited in the literature or can be performed as described below, or can be developed and/or performed in an analogous manner thereof.

As an example for an *in vitro* growth assay, human tumor cell lines, for example HCT116, DLD-1 or MiaPaCa, containing mutated K-ras genes can be used in standard proliferation assays, for example for anchorage dependent growth on plastic or anchorage independent growth in soft agar. Human tumor cell lines are commercially available, for example from ATCC (Rockville MD), and can be cultured according to methods known in the art, for example in RPMI with 10% heat inactivated fetal bovine serum and 200 mM glutamine. Cell culture media, fetal bovine serum and additives are commercially available, for example from Invitrogen/Gibco/BRL (Karlsruhe, Germany) and/or QRH Biosciences (Lenexa, KS). In a standard proliferation assay for anchorage dependent growth, 3 X 10^3 cells can be seeded into 96-well tissue culture plates and allowed to attach, for example overnight at 37 °C in a 5% CO_2 incubator. Compounds can be titrated in media in dilution series and added to 96 well cell cultures. Cells are allowed to grow, for example for 1 to 5 days, typically with a feeding of fresh compound containing media at about half of the time of the growing period, for example on day 3, if the cells are allowed to grow 5 days. Proliferation can be monitored by methods known in the art, such as measuring metabolic activity, for example with standard XTT colorimetric assay (Boehringer

Mannheim) measured by standard ELISA plate reader at OD 490/560, by measuring ^{3}H-thymidine incorporation into DNA following an 8 h culture with 1μCu ^{3}H-thymidine, harvesting the cells onto glass fiber mats using a cell harvester and measuring ^{3}H-thymidine incorporation by liquid scintillation counting, or by staining techniques, such as crystal violet staining. Other suitable cellular assay systems are known in the art.

Alternatively, for anchorage independent cell growth, cells can be plated at 1 x.10^3 to 3 x 10^3 in 0.4% Seaplaque agarose in RPMI complete media, overlaying a bottom layer containing only 0.64% agar in RPMI complete media, for example in 24-well tissue culture plates. Complete media plus dilution series of compounds can be added to wells and incubated, for example at 37 °C in a 5% CO_2 incubator for a sufficient time, for example 10-14 days, preferably with repeated feedings of fresh media containing compound, typically at 3-4 day intervals. Colony formation and total cell mass can be monitored, average colony size and number of colonies can be quantitated according to methods known in the art, for example using image capture technology and image analysis software. Image capture technology and image analysis software, such as Image Pro Plus or media Cybernetics.

As discussed herein, these signaling pathways are relevant for various disorders. Accordingly, by interacting with one or more of said signaling pathways, isoquinoline derivatives are useful in the prevention and/or the treatment of disorders that are dependent from said signaling pathways.

The compounds according to the invention are preferably kinase modulators and more preferably kinase inhibitors. According to the invention, kinases include, but are not limited to one or more Raf-kinases, one or more Tie-kinases, one or more VEGFR-kinases, one or more PDGFR-kinases, p38-kinase and/or SAPK2alpha.

Raf-kinases in this respect are respect preferably include or consist of A-Raf, B-Raf and c-Raf1.

Tie-kinases in this respect preferably include or consist of Tie-2 kinase.

VEGFR-kinases in this respect preferably include or consist of VEGFR-2 kinase.

The compounds according to the invention are more preferably modulators and especially inhibitors of kinases, preferably kinases selected from the group consisting of serine/threonine kinases and receptor tyrosine kinases.

According to the invention, receptor tyrosine kinases are preferably selected from Tie-kinases, VEGFR-kinases, PDGFR-kinases, SAPK-kinases and p38-kinases.

According to the invention, serine/threonine kinases are preferably selected from raf-kinases.

Accordingly, the compounds according to the invention are preferably modulators and more preferably inhibitors of one or more kinases, selected from the group consisting of A-Raf, B-Raf, c-Raf1, Tie-1, Tie-2, Tie-3, VEGFR-1, VEGFR-2, VEGFR-3, p38-kinase and Ltk-kinase.

Due to the kinase modulating or inhibting properties of the compounds according to the invention, the compounds according to the invention preferably interact with one or more signalling pathways which are preferably cell signalling pathways, preferably by downregulating or inhibiting said signaling pathways. Examples for such signalling pathways include, but are not limited to the raf-kinase pathway, the Tie-kinase pathway, the VEGFR-kinase pathway, the PDGFR-kinase pathway, the p38-kinase pathway, the SAPK2alpha pathway and/or the Ras-pathway.

Modulation of the raf-kinase pathway plays an important role in various cancerous and noncancerous disorders, preferably cancerous disorders, such as dermatological tumors, haematological tumors, sarcomas, squamous cell cancer, gastric cancer, head cancer, neck cancer, oesophageal cancer, lymphoma, ovary cancer, uterine cancer and/or prostate cancer. Modulation of the raf-kinase pathway plays a even more important role in various cancer types which show a constitutive activation of the raf-kinase dependent signalling pathway, such as melanoma, colorectal cancer, lung cancer, brain cancer, pancreatic cancer, breast cancer, gynaecological cancer, ovarian cancar, thyroid cancer, chronic leukaemia and acute leukaemia, bladder cancer, hepatic cancer and/or renal cancer. Modulation of the raf-kinase pathway plays also an important role in infection diseases, preferably the infection diseases as mentioned above/below and especially in Helicobacter pylori infections, such as Helicobacter pylori infection during peptic ulcer disease.

One or more of the signalling pathways mentioned above/below and especially the VEGFR-kinase pathway plays an important role in angiogenesis. Accordingly, due to the kinase modulating or inhibting properties of the compounds according to the invention, the compounds according to the invention are suitable for the prophylaxis and/or treatment of pathological processes or disorders caused, mediated and/or propagated by angiogenesis, for example by inducing anti-angiogenesis. Pathological processes or disorders caused, mediated and/or propagated by angiogenesis include, but are not limited to tumors, especially solid tumors, arthritis, especially heumatic or rheumatoid arthritis, diabetic retinopathy, psoriasis, restenosis; fibrotic disorders; mesangial cell proliferative disorders, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, organ transplant rejection, glomerulopathies, metabolic disorders, inflammation and neurodegenerative diseases, and especially solid tumors, rheumatic arthritis, diabetic retinopathy and psoriasis.

Modulation of the p38-signalling pathway plays an important role in various cancerous and although in various noncancerous disorders, such as fibrosis, atherosclerosis, restenosis, vascular disease, cardiovascular disease, inflammation, renal disease and/or angiogenesis, and especially noncancerous disorders such as rheumatoid arthritis, inflammation, autoimmune disease, chronic obstructive pulmonary disease, asthma and/or inflammatory bowel disease.

Modulation of the PDGF-signalling pathway plays an important role in various cancerous and although in various noncancerous disorders, such as rheumatoid arthritis, inflammation, autoimmune disease, chronic obstructive pulmonary disease, asthma and/or inflammatory bowel disease, and especially noncancerous disorders such as fibrosis, atherosclerosis, restenosis, vascular disease, cardiovascular disease, inflammation, renal disease and/or angiogenesis.

Subject of the present invention are therefore isoquinoline derivatives according to the invention as promoters or inhibitors, preferably as inhibitors, of the signaling pathways described herein. Preferred subject of the invention are therefore isoquinoline derivatives according to the invention as promoters or inhibitors, preferably as inhibitors of the raf-kinase pathway. More preferred subject of the invention are therefore isoquinoline derivatives according to the invention as promoters or inhibitors, preferably as inhibitors of the raf-kinase. Even more preferred subject of the invention are isoquinoline derivatives according to invention as promoters or inhibitors, preferably as inhibitors of one or more raf-kinases, selected from the group consisting of A-raf, B-raf and c-raf1. Especially preferred subject of the invention are isoquinoline derivatives according to the invention as promoters or inhibitors, preferably as inhibitors of c-raf1.

Thus, subject of the present invention are isoquinoline derivatives according to the invention as medicaments. Subject of the present invention are isoquinoline derivatives according to the invention as medicament active ingredients. Further subject of the present invention is the use of one or more isoquinoline derivatives according to the invention as a pharmaceutical. Further subject of the present invention is the use of one or more isoquinoline derivatives according to the invention in the treatment and/or the prophylaxis of disorders, preferably the disorders described herein, more preferred disorders that are caused, mediated and/ or propagated by signalling pathways discussed herein, even more preferred disorders that are caused, mediated and/or propagated by raf-kinases and especially disorders that are caused, mediated and/or propagated by raf-kinases, selected from the group consisting of A-raf, B-raf and c-raf1. Usually, the disorders discussed herein are divided into two groups, hyperproliferative and non hyperproliferative disorders. In this context, psioarsis, arthritis, inflammation, endometriosis, scarring, begnin prostatic hyperplasia, immunological diseases, autoimmune diseases and immunodeficiency diseases are to be regarded as noncancerous disorders, of which arthritis, inflammation, immunological diseases, autoimmune diseases and immunodeficiency diseases are usually regarded as non hyperproliferative disorders. In this context, brain cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, gynaecological cancer, thyroid cancer, lymphoma, chronic leukaemia and acute leukaemia are to be regarded as cancerous disorders, all of which are usually regarded as hyperproliferative disorders. Especially cancerous cell growth and especially cancerous cell growth mediated by raf-kinase is a disorder which is a target of the present invention. Subject of the present invention therefore are isoquinoline derivatives according to the invention as medicaments and/or medicament active ingredients in the treatment and/or the prophylaxis of said disorders and the use of isoquinoline derivatives according to the invention for the manufacture of a pharmaceutical for the treatment and/or

the prophylaxis of said disorders as well as a method of treatment of said disorders, comprising administering one or more isoquinoline derivatives according to the invention to a patient in need of such an administration.
Subject of the present invention therefore are isoquinoline derivatives according to the invention as medicaments and/or medicament active ingredients in the treatment and/or the prophylaxis said disorders and the use of isoquinoline derivatives according to the invention for the manufacture of a pharmaceutical for the treatment and/or the prophylaxis of said disorders as well as a method of treatment of said disorders, comprising administering one or more isoquinoline derivatives according to the invention to a patient in need of such an administration.

Accordingly, subject of the present invention are pharmaceutical compositions that contain one or more isoquinoline derivatives according to the invention. Subject of the present invention are especially pharmaceutical compositions that contain one or more isoquinoline derivatives according to the invention and one or more additional compounds (other than the compounds of the instant invention), preferably selected from the group consisting of physiologically acceptable excipients, auxiliaries, adjuvants, carriers and pharmaceutically active ingredients other than the compounds according to the invention.
Accordingly, subject of the present invention is a process for the manufacture of a pharmaceutical composition, wherein one or more isoquinoline derivatives according to the invention and one or more compounds (other than the compounds of the instant invention), preferably selected from the group consisting of carriers, excipients, auxiliaries, adjuvants and pharmaceutically active ingredients other than the compounds according to the invention.

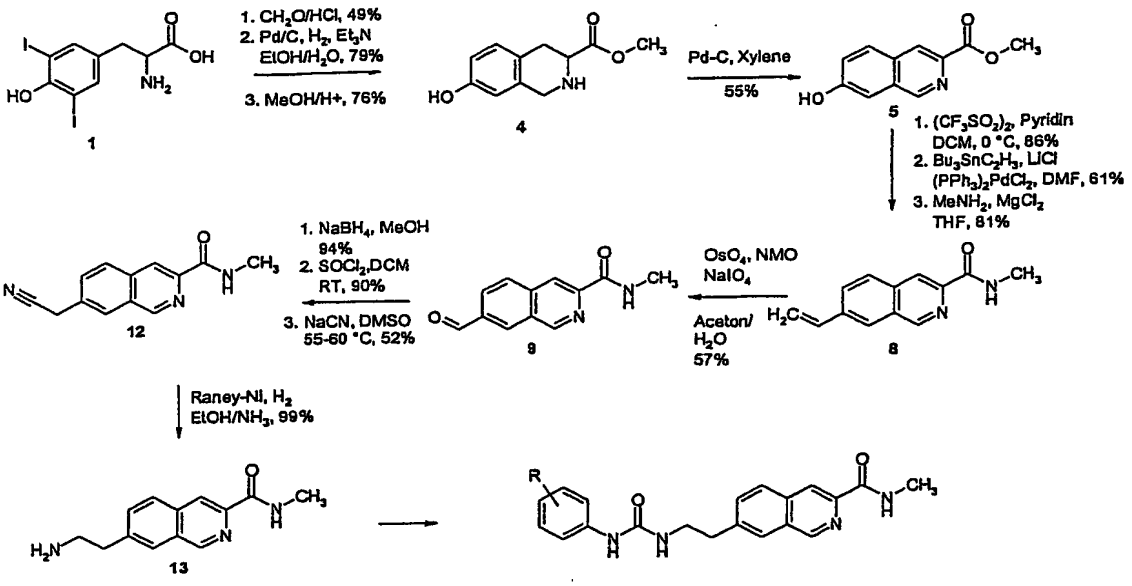
Accordingly, the use of the compounds according to the invention in the treatment of Hyperproliferative disorders is a subject of the instant invention.

Accordingly, the use of the compounds according to the invention for producing a medicament for the treatment of hyperproliferative disorders is a subject of the instant invention.

Above and below, all temperatures are given in °C. In the examples below, "conventional work-up" means that the organic phase is washed with saturated $NaHCO_3$ solution, if desired with water and saturated NaCl solution, the phases are separated, the organic phase is dried over sodium sulfate and evaporated, and the product is purified by chromatography on silica gel, by preparative HPLC and/or by crystallization.

The present invention relates to isoquinoline derivatives of formula I, the use of the compounds of formula I as inhibitors of raf-kinase, the use of the compounds of formula I for the manufacture of a pharmaceutical composition and a method of treatment, comprising administering said pharmaceutical composition to a patient..

Experimental part



250 g (0.58 mol) of 3,5-diiodotyrosine **1** were suspended in 2.5 l of conc. hydrochloric acid with stirring, 239 ml (2.31 mol) of ethylene glycol dimethyl ether and 171.8 ml (2.31 mol) of formaldehyde solution (37%) were added, and the mixture was stirred at 65°C for a total of 55 hours. The reaction mixture was cooled in an ice-water bath, and the precipitate was filtered off with suction and rinsed with 200 ml of water and 400 ml of hydrochloric acid. The cream-coloured filter cake was suspended in 600 ml of hydrochloric acid, filtered off with suction, rinsed with water, dried in air and then dried at 40°C in a vacuum drying cabinet. Further product was obtained from the mother liquor by crystallisation.

Yield: 129.6 g (51%) of **2**, beige solid

124.5 g (251.8 mmol) of **2** were hydrogenated at 4 bar and room temperature using 18 g of Pd/C (5%) in 1.7 l of ethanol and 450 ml of water with addition of 140 ml of triethylamine. The solution was freed from catalyst and evaporated on a rotary evaporator until crystallisation commenced and then stored overnight at 4°C in the refrigerator. The precipitated crystals were filtered off with suction, rinsed with cold water and subsequently dried at 40°C under reduced pressure.

Yield: 36.7 g (75%) of **3**, beige solid

15.5 g (80.4 mmol) of **3** were suspended in 150 ml of methanol at room temperature, and 9.4 ml (176.8 mmol) of conc. H_2SO_4 were added. The clear solution formed after the addition was refluxed for 18 hours. The reaction mixture was cooled to room temperature and subsequently adjusted to pH = 6-7 using 16.5 ml of NaOH (32%) with stirring, during which a very fine precipitate formed. The reaction mixture was evaporated to about 10-20% of its volume. About 500 ml of ethyl acetate and Na_2SO_4 were added to the viscous residue obtained in this way, and the mixture was heated to the boil. The hot suspension was filtered with suction, and the residue was rinsed with about 100 ml of ethyl acetate. About 300 ml of acetone were added to the residue, and the mixture was heated to the boil with stirring. After 10 minutes, the hot suspension was filtered with suction, and the residue was rinsed with about 50 ml of acetone. The filtrates were combined and evaporated to dryness.

Yield: 13.5 g (81%) of **4**, beige solid

1.75 g (7.85 mmol) of **4** were dissolved in 10 ml of DMF and 60 ml of xylene and heated to the boiling point, and 1.4 g of Pd/C (10%) were added. The reaction mixture was refluxed for 3 hours and then filtered while hot, and the residue was rinsed with 5 ml of hot DMF. The filtrate was evaporated, and the residue was purified by chromatography (120 g of silica gel, eluent: DCM/MeOH (100:0 – 95:5 in 75 minutes).

Yield: 1.3 g (80%) of **5**, pale-yellow solid

2.43 g (11.96 mmol) of **5** were suspended in 60 ml of dichloromethane and 1.26 ml of pyridine at 0°C, and 2.21 ml (13.16 mmol) of trifluoromethanesulfonic anhydride were subsequently added slowly. The dark-red, clear solution formed was stirred at 0 – 5°C for a further 1 hour. The reaction mixture was extracted 3x with 30 ml of water each time and 1x with 30 ml of saturated NaCl solution, dried using Na_2SO_4, filtered and evaporated. The residue was digested with petroleum ether/diethyl ether

(1:1), filtered off with suction, rinsed with petroleum ether/diethyl ether (2:1) and dried under reduced pressure. Further product was obtained from the mother liquor by chromatography (35 g of silica gel, eluent: ethyl acetate/petroleum ether 7:3).

Yield: 3.82 g (94%) of **6**, beige solid

4 g (11.93 mmol) of **6**, 3.64 g of lithium chloride (85.9 mmol) and 164.9 mg of bis(triphenylphosphine)palladium chloride (0.24 mmol) were dissolved in 30 ml of DMF under argon, and 3.48 ml (11.93 mmol) of tributylvinylstannane were added. The reaction mixture was stirred at 90°C for 1 hour and subsequently evaporated in a rotary evaporator. The residue was taken up in 300 ml of water and extracted with ethyl acetate (3 x 70 ml). The combined organic phases were washed 1x with 30 ml of saturated NaCl solution, dried using Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (300 g of silica gel, eluent: dichloromethane/methanol (2.5%).

Yield: 1.73 g (67%) of **7**, yellow solid

1.73 g (8.03 mmol) of **7** and 382.4 mg (4.02 mmol) of magnesium chloride were dissolved in 5 ml of THF, and 40.2 ml of methylamine (1 M in THF, 40.2 mmol) were added slowly. The reaction mixture was stirred at room temperature for 4 hours and evaporated in a rotary evaporator. The residue was taken up in ethyl acetate, extracted 2x with water and 1x with saturated NaCl solution, dried using Na_2SO_4, filtered and evaporated to about 20%, during which a precipitate formed. This was filtered off with suction, rinsed with diethyl ether and dried. Further product was obtained from the mother liquor by evaporation and digestion of the residue with diethyl ether/ethyl acetate (8:2), subsequent filtration with suction and rinsing with diethyl ether.

Yield: 1.4 g (81%) of **8**, beige solid

774 mg (6.6 mmol) of N-methylmorpholine N-oxide were dissolved in 2 ml of water at room temperature, 152.7 mg (0.6 mmol) of osmium tetraoxide were

added, and a solution of 1.29 g (6 mmol) of **8** in 12 ml of acetone was subsequently added dropwise. The reaction mixture changed colour to dark green, and a precipitate formed. 2.57 g (12 mmol) of sodium metaperiodate were added, and the reaction mixture was diluted with 2 ml of water and 8 ml of acetone and stirred overnight at room temperature. The precipitate was filtered off with suction and rinsed with acetone. The filtrate was evaporated, and the residue was taken up in ethyl acetate and washed 1x with water and 1x with saturated NaCl solution, dried using Na_2SO_4, filtered and evaporated. The residue was digested with diethyl ether/petroleum ether (2:1), filtered off with suction, rinsed with petroleum ether and subsequently dried under reduced pressure.
Yield: 734 mg (55%) of **9**, colourless solid

0.5 g (2.33 mmol) of **9** was suspended in 5 ml of methanol and cooled to 0°C, and 48.6 mg (1.28 mmol) of sodium borohydride were added. After 1 minute, a clear, yellowish solution had formed. 642 µl of 1 N NaOH were added to the reaction mixture, during which a precipitate formed. The reaction mixture was diluted with ethyl acetate and water, and the precipitate was filtered off with suction, rinsed with water and ethyl acetate and subsequently dried at 40°C under reduced pressure. The filtrate was transferred into a separating funnel, the aqueous phase was separated off, and the organic phase was washed 1x with water and 1x with saturated NaCl solution, dried using Na_2SO_4, filtered and evaporated. A precipitate had also formed from the aqueous phase. This was filtered off with suction, washed with water and subsequently dried at 40°C under reduced pressure. All isolated products were identical and were combined.
Yield: 427 mg (79.5%) of **10**, colourless solid

330 mg (1.45 mmol) of **10** were suspended in 10 ml of dichloromethane at room temperature under argon, and 158 µl (2.18 mmol) of thionyl chloride were added. After the mixture had been stirred at room temperature for 30 minutes, a further 16 µl (0.22 mmol) of thionyl chloride were added, and the

mixture was stirred for a further 1 hour. The reaction mixture was diluted with dichloromethane, extracted 1x with saturated $NaHCO_3$ solution, 1x with water and 1x with saturated NaCl solution, dried using Na_2SO_4, filtered and evaporated.

Yield: 331 mg (90.5%) of **11**, colourless solid

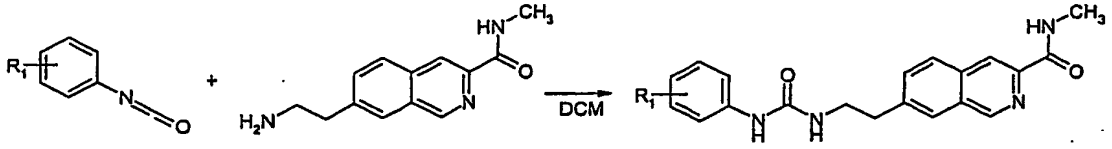
426 mg (1.67 mmol) of **11** and 90 mg (1.84 mmol) of sodium cyanide were dissolved in 4 ml of dimethyl sulfoxide and stirred at 55-60°C. After the mixture had been stirred for 2 hours, a further 41 mg (0.83 mmol) of sodium cyanide were added, and the solution was stirred for a further 1 hour. The reaction mixture was diluted with 40 ml of water and extracted 3x with ethyl acetate. The combined organic phases were washed 1x with water and 1x with saturated NaCl solution, dried using Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (10 g of silica gel, eluent: DCM/MeOH 100:0 – 95:5 in 60 minutes).

Yield: 200 mg (48%) of **12**, pale-brown oil, crystallises on standing

Compound **12** was hydrogenated overnight at 45°C and 5 bar using Raney nickel in methanolic ammonia solution. The reaction solution was filtered through kieselguhr, the filter cake was rinsed with MeOH, and the filtrate was subsequently evaporated. The residue was taken up in 1 ml of acetonitrile and 0.5 ml of water, frozen and freeze-dried overnight.

Yield: 201 mg (99%) of **13**, pale-brown oil, crystallises on standing

Synthesis of the ureas

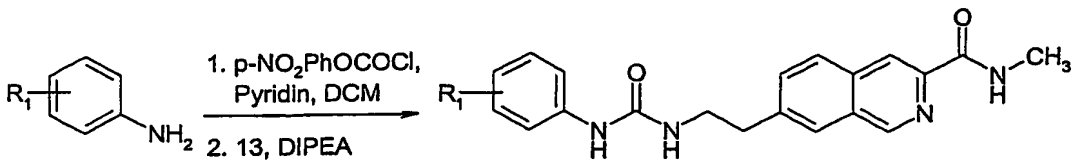


Variant A

40 µmol of isocyanate together with 40 µmol of amine **13** were dissolved in dichloromethane and stirred at room temperature for 3 hours. The reaction mixture was evaporated to dryness, and the residue was purified by

chromatography (4 g of silica gel, eluent: DCM/MeOH 100:0 – 95:5 in 45 minutes). The product obtained in this way was taken up in 1.5 ml of acetonitrile: water = 2:1, frozen and freeze-dried overnight.

Variant B

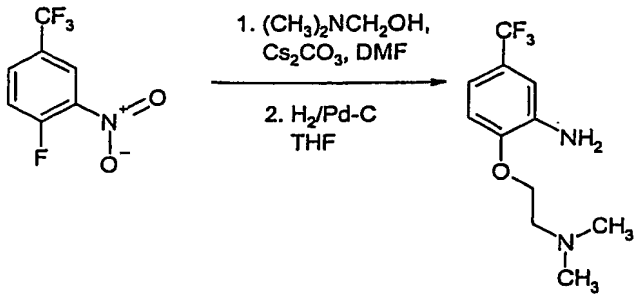


79 µmol of aniline were dissolved in dichloromethane, treated successively with 87 µmol of pyridine and 87 µmol of p-nitrophenyl chloroformate, and stirred at room temperature. When the reaction was complete, 79 µmol of **13** and 158 µmol of DIPEA were added, and the reaction mixture was stirred at room temperature. The reaction mixture was diluted with dichloromethane, extracted successively 1x with water, 1x with 1N NaOH and 2x with water, dried using Na_2SO_4, filtered and evaporated. The crude product obtained in this way was purified by the following variants:

Variant A: The residue was purified by column chromatography (4 g of silica gel, eluent: DCM/MeOH 0-5% in 45 minutes or 3-6% in 45 minutes). The product obtained in this way was taken up in 1 ml of acetonitrile:water = 2:1, frozen and freeze-dried overnight.

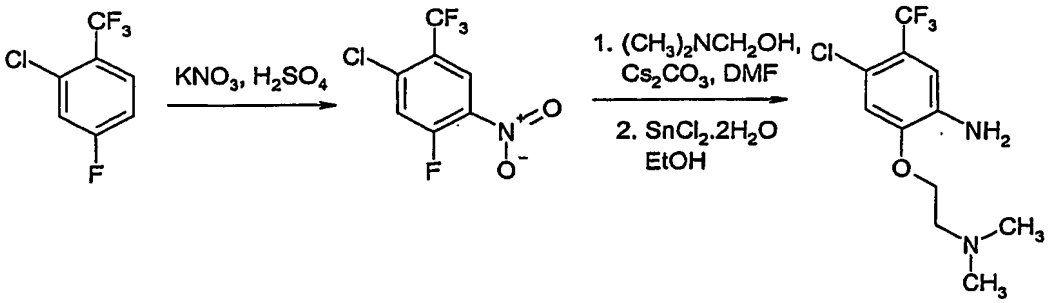
Variant B: The residue was digested with ethyl acetate, filtered off with suction, rinsed with ethyl acetate and diethyl ether and subsequently dried overnight under reduced pressure.

Synthesis of the anilines



3.45 ml (23.91 mmol) of 4-fluoro-3-nitrobenzotrifluoride were dissolved in 100 ml of dimethylformamide, 3.63 ml (35.87 mmol) of 2-(dimethylamino)ethanol and 18.1 g (55 mmol) of caesium carbonate were added, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, washed 1x with water and 1x with saturated NaCl solution, dried using Na_2SO_4, filtered, entrained a number of times with toluene in a rotary evaporator and subsequently evaporated to dryness. The residue was purified by chromatography (120 g of silica gel, eluent: dichloromethane:acetone = 100:0 to 90:10).
Yield: 5.8 g (85%), yellow oil

The nitro compound obtained in this way was hydrogenated overnight at room temperature in THF using H_2 and Pd/C (5%). The catalyst was filtered off, and the filtrate was evaporated to dryness.
Yield: 5 g (98%), yellow crystals



46 g (227 mmol) of 2-chloro-4-fluorobenzotrifluoride were dissolved in 460 ml of conc. sulfuric acid and cooled to between -5 and 0°C in an ice-water bath. 27.55 g (272.5 mmol) of potassium nitrate were added to this solution in portions. After 30 minutes, the reaction mixture was warmed to room temperature and stirred for 22 hours. The reaction mixture was poured onto ice and extracted 3x with ethyl acetate. The combined organic phases were washed 1x with saturated $NaHCO_3$ solution and 1x with saturated NaCl solution, dried using sodium sulfate, filtered and evaporated. The residue crystallised on standing overnight. The crystals were digested with a little petroleum ether, filtered off with suction and dried under reduced pressure. Yield: 48.8 g (88%), pale-yellow crystals

2.25 g (9.24 mmol) of 5-chloro-4-fluoro-3-nitrobenzotrifluoride together with 1.87 ml (18.48 mmol) of 2-(dimethylamino)ethanol and 7 g (21.25 mmol) of caesium carbonate were dissolved in dimethylformamide and stirred at room temperature for 3 hours. The reaction mixture was filtered, and the residue was rinsed with dichloromethane. The filtrate was diluted with dichloromethane, washed 3x with water and 1x with saturated NaCl solution, dried using Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (120 g of silica gel, eluent: DCM/MeOH 0-5% in 45 minutes). The product isolated in this way was again taken up in dichloromethane, washed 1x with 1N NaOH, 2x with water and 1x with saturated NaCl solution, dried using Na_2SO_4, filtered and evaporated. Yield: 1.59 g (54%) of a yellow oil, crystallises on standing

100 mg (0.3 mmol) of the nitro compound were reduced at 70°C for 1 hour in ethanol using 360 mg (1.6 mmol) of tin(II) chloride dihydrate. The reaction mixture was rendered basic using saturated $NaHCO_3$ solution. The precipitate was filtered off through kieselguhr with suction and rinsed with ethanol and ethyl acetate. The filtrate was evaporated to an aqueous residue in a rotary evaporator and extracted 3x with ethyl acetate. The combined

organic phases were washed 1x with saturated NaCl solution, dried using Na_2SO_4, filtered and evaporated.
Yield: 87 mg (90%) of a brown oil

The following compounds are prepared according to the methods as described herein or in an anlogous manner thereof:
7-(2-{3-[(2-Dimethylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-ethyl)-isoquinoline-3-carboxylic acid methylamide;
7-{2-[3-(4-Methyl-3-trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;
7-{2-[3-(3-Trifluoromethanesulfonyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;
7-{2-[3-(3-Trifluoromethoxy-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;
7-{2-[3-(4-Fluoro-3-trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;
7-{2-[3-(4-Trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;
7-{2-[3-(3-Trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;
7-{2-[3-(2-Methoxy-5-trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;
7-{2-[3-(5-Chloro-2-methoxy-4-methyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide;
7-{2-[3-(4-Chloro-2-methoxy-5-trifluoromethyl-phenyl)-ureido]-ethyl}-isoquinoline-3-carboxylic acid methylamide.

Retention times (Rt) as disclosed herein are, if not indicated otherwise, HPLC retention times, obtained according the following methods:

General Method:
Gradient: 5.5 min; flow rate: 2.75 ml/min from 90:10 to 0:100 H_2O/ACN

Water + TFA (0.01% by vol.); acetonitrile + TFA (0.01% by vol.)
Column: Chromolith SpeedROD RP 18e 50-4.6
Wavelength: 220 nm.

The compounds disclosed herein can preferably be produced according to the procedures described herein or in an analogous manner thereof.

Example A: Injection vials

A solution of 100 g of an active compound of the formula I and 5 g of disodium hydrogenphosphate is adjusted to pH 6.5 in 3 l of double-distilled water using 2N hydrochloric acid, sterile-filtered, dispensed into injection vials, lyophilized under sterile conditions and aseptically sealed. Each injection vial contains 5 mg of active compound.

Example B: Suppositories

A mixture of 20 g of an active compound of the formula I is fused with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active compound.

Example C: Solution

A solution of 1 g of an active compound of the formula I, 9.38 g of $NaH_2PO_4 \cdot 2\ H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12\ H_2O$ and 0.1 g of benzalkonium chloride in 940 ml of double-distilled water is prepared. It is adjusted to pH 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

500 mg of an active compound of the formula I is mixed with 99.5 g of petroleum jelly under aseptic conditions.

Example E: Tablets

A mixture of 1 kg of active compound of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed to give tablets in a customary manner such that each tablet contains 10 mg of active compound.

Example F: Coated tablets

Analogously to Example E, tablets are pressed and are then coated in a customary manner using a coating of sucrose, potato starch, talc, tragacanth and colourant.

Example G: Capsules

2 kg of active compound of the formula I are dispensed into hard gelatin capsules in a customary manner such that each capsule contains 20 mg of the active compound.

Example H: Ampoules

A solution of 1 kg of active compound of the formula I in 60 l of double-distilled water is sterile-filtered, dispensed into ampoules, lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 10 mg of active compound.